Cemdisiran, an Investigational RNAi Therapeutic in Development for the Treatment of IgA Nephropathy (IgAN) and Other Complement-Mediated Diseases

RNAi ROUNDTABLE 2022

Alnylam®@20

September 27, 2022

Agenda

Welcome
- Chris Brickley – Associate Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

Overview of Cemdisiran Program
- Sonalee Agarwal, Ph.D. – Vice President and Program Leader, Cemdisiran

IgAN Disease Background, Treatment Landscape, and Unmet Need
- Jonathan Barratt, Ph.D., FRCP – The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences; Honorary Consultant Nephrologist, The John Walls Renal Unit, Leicester General Hospital

Cemdisiran Phase 2 Data
- Ishir Bhan, M.D., MPH – Senior Director, Clinical Research

Q&A Session

Reminders

Event will run for approximately 60 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at https://capella.alnylam.com

Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including but not limited to expectations regarding our aspiration to become a top-tier biotech company, the potential of cemdisiran to address several complement-mediated diseases, either alone or in combination with other investigational therapeutics, and the potential of further evaluation of cemdisiran as a potential therapy in IgAN. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the recent leadership transition on our ability to attract and retain talent and to successfully execute on our "*Alnylam P^{5}x25*" strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates, including vutrisiran and patisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran and patisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO, AMVUTTRA and OXLUMO in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

Agenda

Welcome
- Chris Brickley – Associate Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

Overview of Cemdisiran Program
- Sonalee Agarwal, Ph.D. – Vice President and Program Leader, Cemdisiran

IgAN Disease Background, Treatment Landscape, and Unmet Need
- Jonathan Barratt, Ph.D., FRCP – The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences; Honorary Consultant Nephrologist, The John Walls Renal Unit, Leicester General Hospital

Cemdisiran Phase 2 Data
- Ishir Bhan, M.D., MPH – Senior Director, Clinical Research

Q&A Session

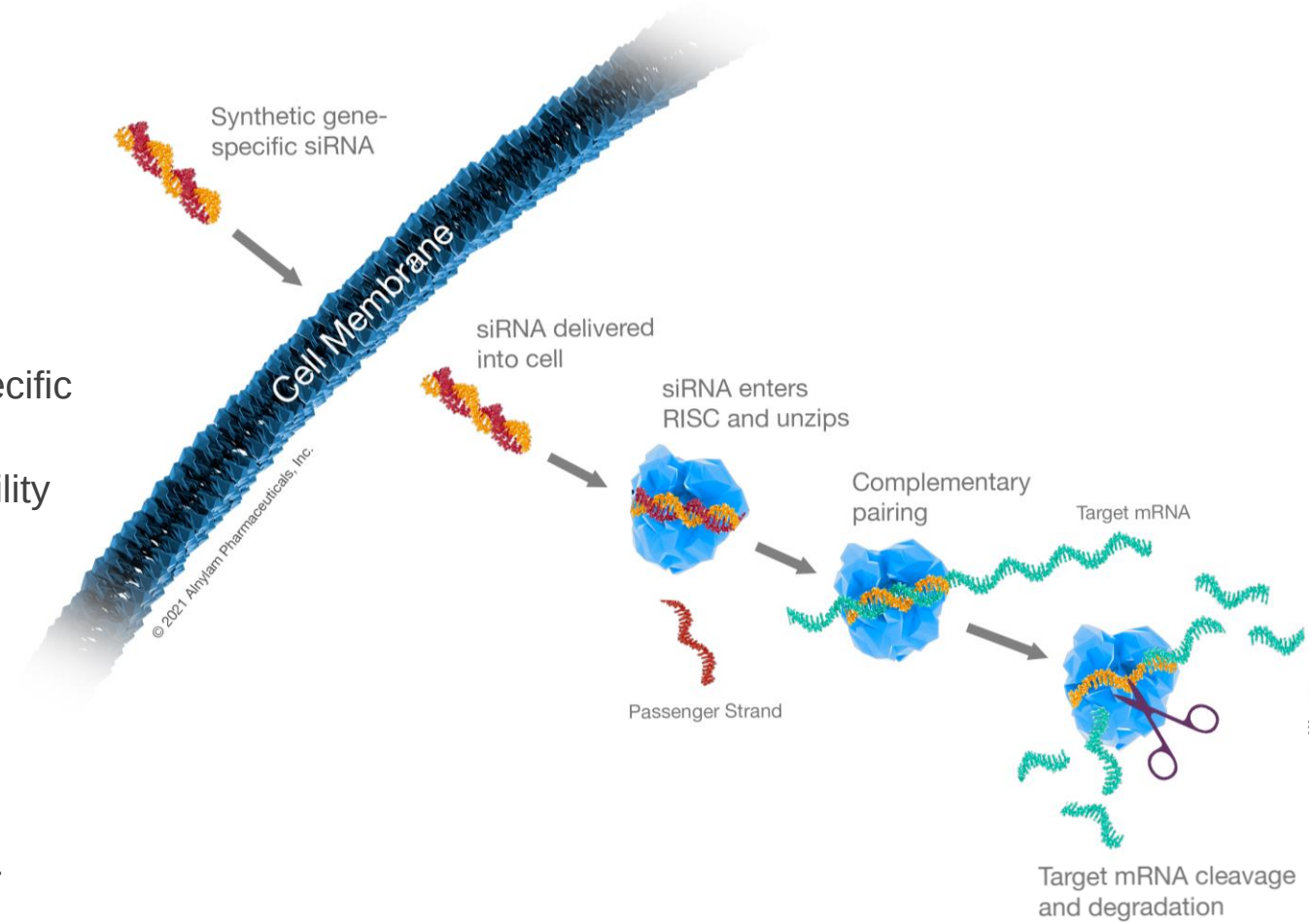
Alnylam Poised to Become a Top-Tier Biotech

Leader in RNAi Therapeutics

- Pioneered **new class of innovative medicines**
- **5** medicines approved in **< 4 years**
- Robust clinical pipeline across rare and prevalent diseases
- **Global footprint** with strong commercial capabilities
- Leading IP estate with fundamental, delivery, and product-specific patent protection
- Strong balance sheet, on path toward financial self-sustainability

Highly differentiated with proven track record and derisked GalNAc platform

- Modular and reproducible approach to drug development
- Historic probability of clinical success with liver targeted RNAi therapeutics multiples higher than industry standards
- **Organic product engine** capable of sustaining innovation for future growth
- Track record of setting and exceeding 5-year goals



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis with PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
LEQVIO (inclisiran)	*Hypercholesterolemia*[5]			●	Milestones & up to 20% Royalties[6]
amvuttra (vutrisiran)	*hATTR Amyloidosis with PN*[7]			●	Global
Patisiran	*ATTR Amyloidosis with CM*		●		Global
Vutrisiran	*ATTR Amyloidosis with CM*		●		Global
Vutrisiran[8]*	*Stargardt Disease*		○		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●		●	Global
Cemdisiran (+/- Pozelimab)[9]*	*Complement-Mediated Diseases*		●		50-50; Milestone/Royalty
Belcesiran[10]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[11]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50
ALN-APP*	*Alzheimer's Disease;* *Cerebral Amyloid Angiopathy*	●			50-50
ALN-XDH*	*Gout*	●			Global

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia; [6] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [7] Approved in the U.S. for the PN of hATTR amyloidosis in adults [8] Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022; [9] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [10] Dicerna is leading and funding development of belcesiran; [11] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of September 2022

Agenda

Welcome
- Chris Brickley – Associate Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

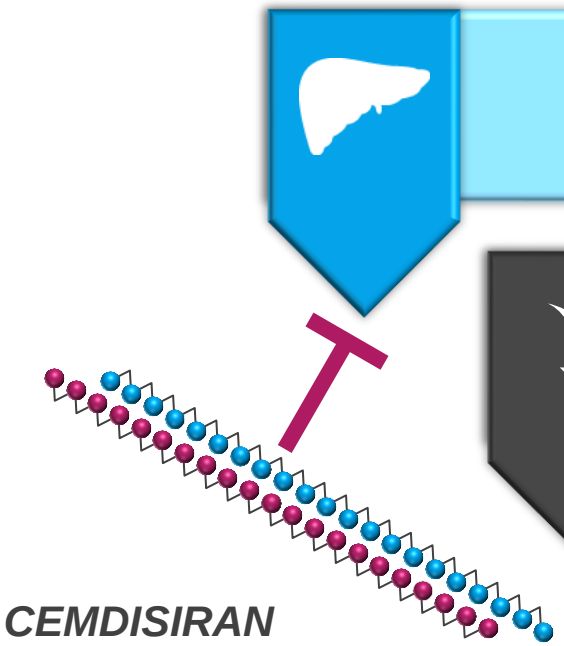
Overview of Cemdisiran Program
- Sonalee Agarwal, Ph.D. – Vice President and Program Leader, Cemdisiran

IgAN Disease Background, Treatment Landscape, and Unmet Need
- Jonathan Barratt, Ph.D., FRCP – The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences; Honorary Consultant Nephrologist, The John Walls Renal Unit, Leicester General Hospital

Cemdisiran Phase 2 Data
- Ishir Bhan, M.D., MPH – Senior Director, Clinical Research

Q&A Session

RNAi Therapeutic Hypothesis in Complement-Mediated Diseases



Production of C5 in liver

Reduce
Activity of terminal pathway of complement

Reduce
Circulating C5 by 99%

Reduce or Halt
Inflammation and tissue damage

Cemdisiran* Has Potential to Address Several Complement-Mediated Diseases

Studies Ongoing Evaluating Cemdisiran Alone or in Combination with MAb

Cemdisiran Monotherapy

IgA Nephropathy

Cemdisiran Combination Therapy

Myasthenia Gravis
Prevalence ~175K
Therapeutic Objective to Improve Motor Function & Activities of Daily Living

PNH
Prevalence ~25K
Therapeutic Objective to Reduce RBC hemolysis

Evaluating Role for Cemdisiran Monotherapy

- Sub-maximal levels of complement inhibition may be effective
- Positive results from Phase 2 study
- Opportunity to expand to other renal diseases involving complement

Evaluating Role for Combination Therapy with Cemdisiran + Pozelimab**

- Potent inhibition of C5 required
- Phase 3 studies underway
- Opportunity to expand to other complement-driven diseases

* Cemdisiran is an investigational RNAi therapeutic and has not been approved by the FDA, EMA, or any other regulatory agency. No conclusions can or should be drawn regarding its safety or effectiveness in this population

** Pozelimab is an investigational anti-C5 monoclonal antibody in development by Regeneron; combination studies being led by Regeneron

Cemdisiran/Pozelimab Combination Phase 3 Studies

Clinical Activities Led by Regeneron

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Phase 3 Study[1]

Study in PNH Naïve patients

Study Enrolling

Phase 3 Study[2]

Study of pozelimab and cemdisiran combination therapy in adult patients with PNH who switch from eculizumab therapy

Study Enrolling

Myasthenia Gravis (MG)

Phase 3 Study[3]

Study in adult patients with Myasthenia Gravis

Study Enrolling

[1]NCT05133531; [2]NCT05131204; [3]NCT05070858

IgA Nephropathy (IgAN)

Most Common Primary Chronic Glomerular Disease in World

Description

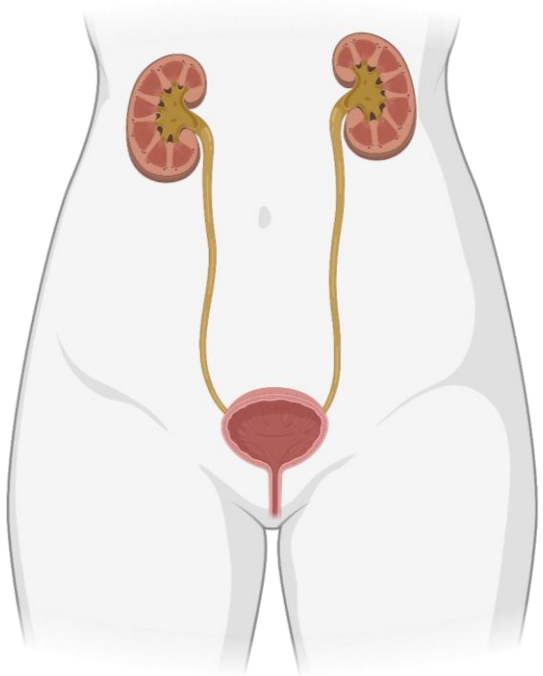
Clinical features include proteinuria, hematuria, kidney injury and long-term progression to end-stage renal disease (ESRD)

IgAN Cases[1-5]

~350,000 – 450,000

US + EU + Japan*

Up to 40% of patients progress to ESRD[6,7]



- Hematuria
- Proteinuria
- Kidney function
- Kidney failure

* Based on Alnylam internal calculations

1. Kwon CS, et al. J Health Econ Outcomes Res. 8(2):36-45.; 2. Schena FP, et al. Semin Nephrol. 2018;38(5):435-442.; 3. Census Population Clock. Census.gov. September 14, 2022.; 4. Moriyama T, et al. PLoS ONE. 2014;9(3):e91756.; 5. Alnylam Pharmaceuticals, Data on File. 6. Lai KN, Tang SC, Schena FP et al. Nature Reviews Disease Primers. 2016;2:16001; 7. Wyatt RJ, Julian BA, Baehler RW et al. J Am Soc Nephrol 1998; 9(5); 853-8

Agenda

Welcome
- Chris Brickley – Associate Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

Overview of Cemdisiran Program
- Sonalee Agarwal, Ph.D. – Vice President and Program Leader, Cemdisiran

IgAN Disease Background, Treatment Landscape, and Unmet Need
- Jonathan Barratt, Ph.D., FRCP – The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences; Honorary Consultant Nephrologist, The John Walls Renal Unit, Leicester General Hospital

Cemdisiran Phase 2 Data
- Ishir Bhan, M.D., MPH – Senior Director, Clinical Research

Q&A Session

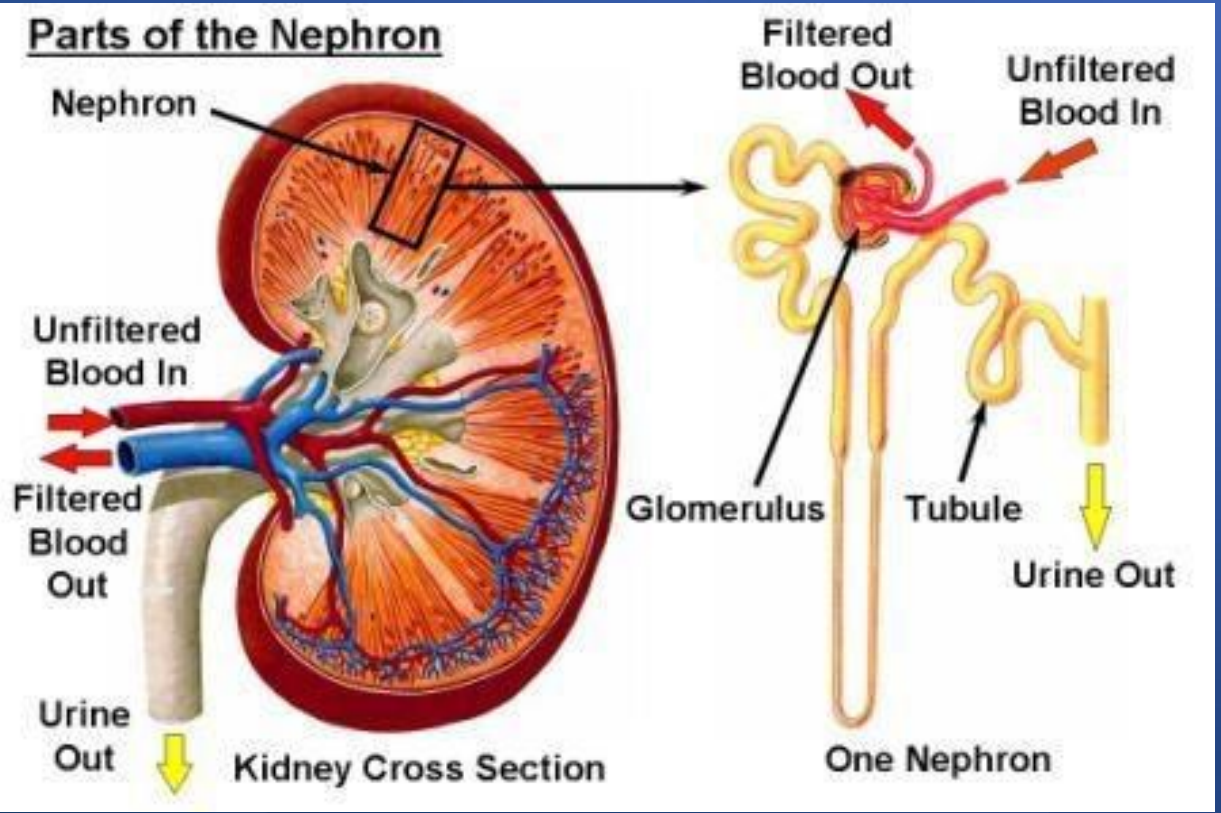
UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

IgA nephropathy

Current developments
&
treatment options

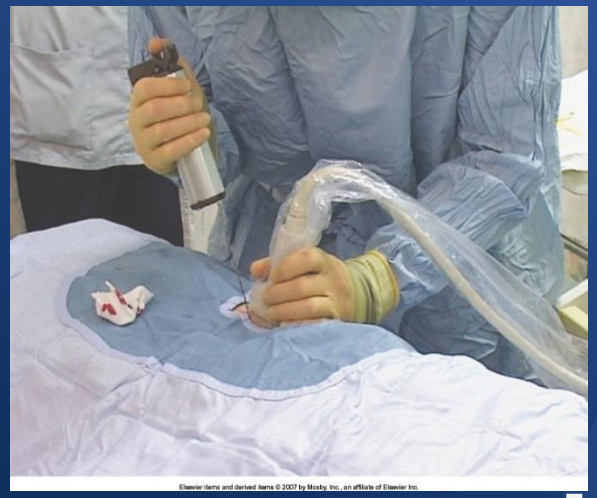
Professor Jonathan Barratt
University of Leicester
&
John Walls Renal Unit, Leicester

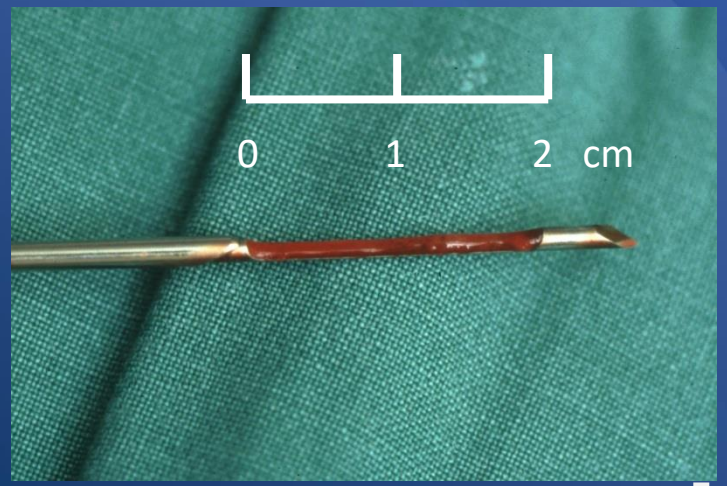


From Ancient Greek νεφρός (*nephrós*, “kidney”)

UNIVERSITY OF LEICESTER

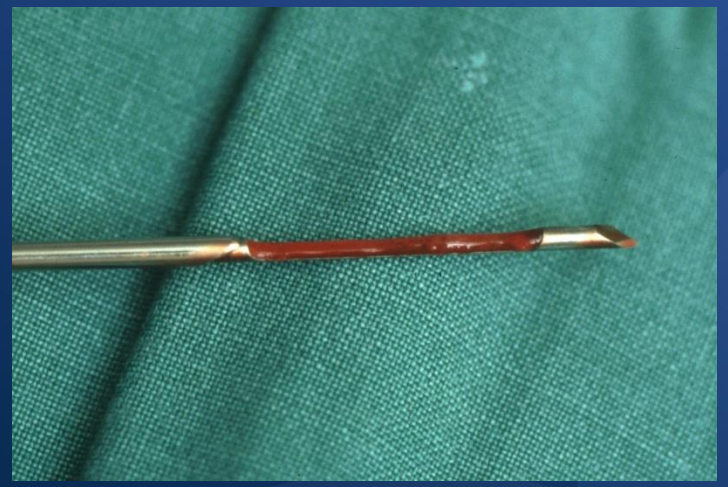
Leicester IgA Nephropathy Research Group

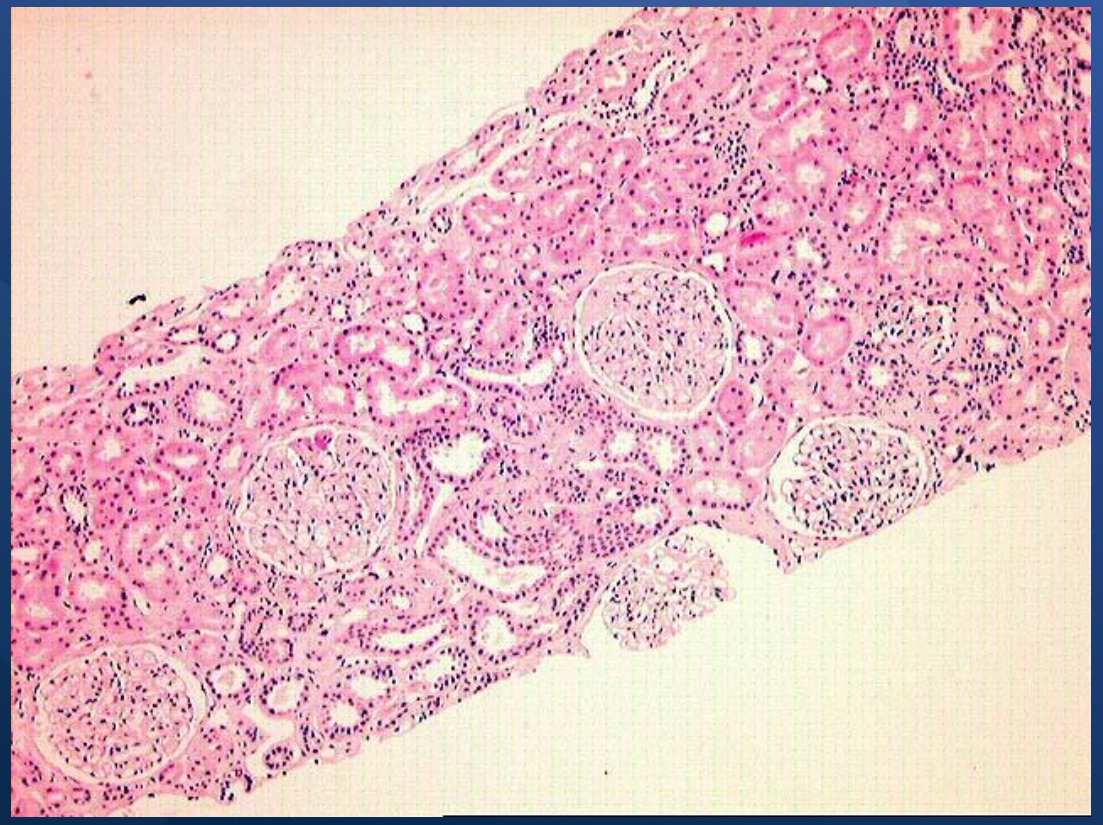


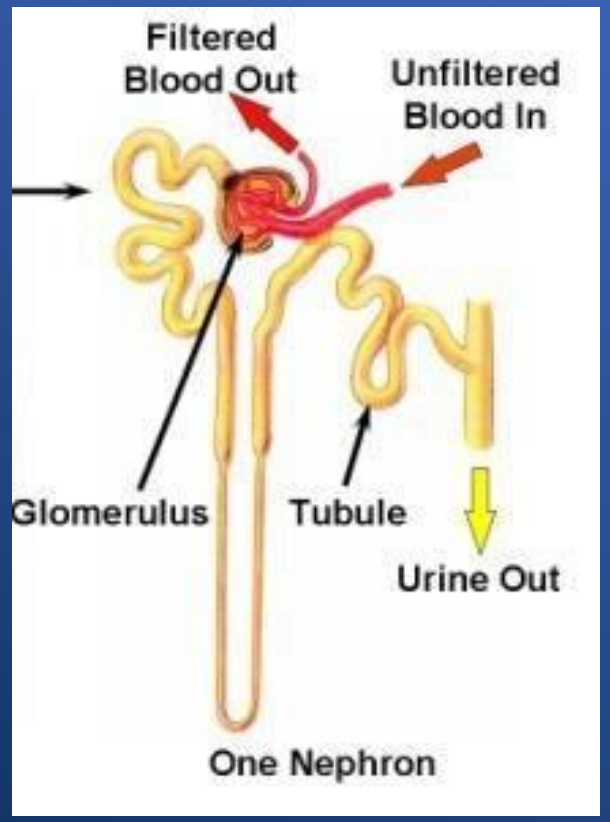


UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

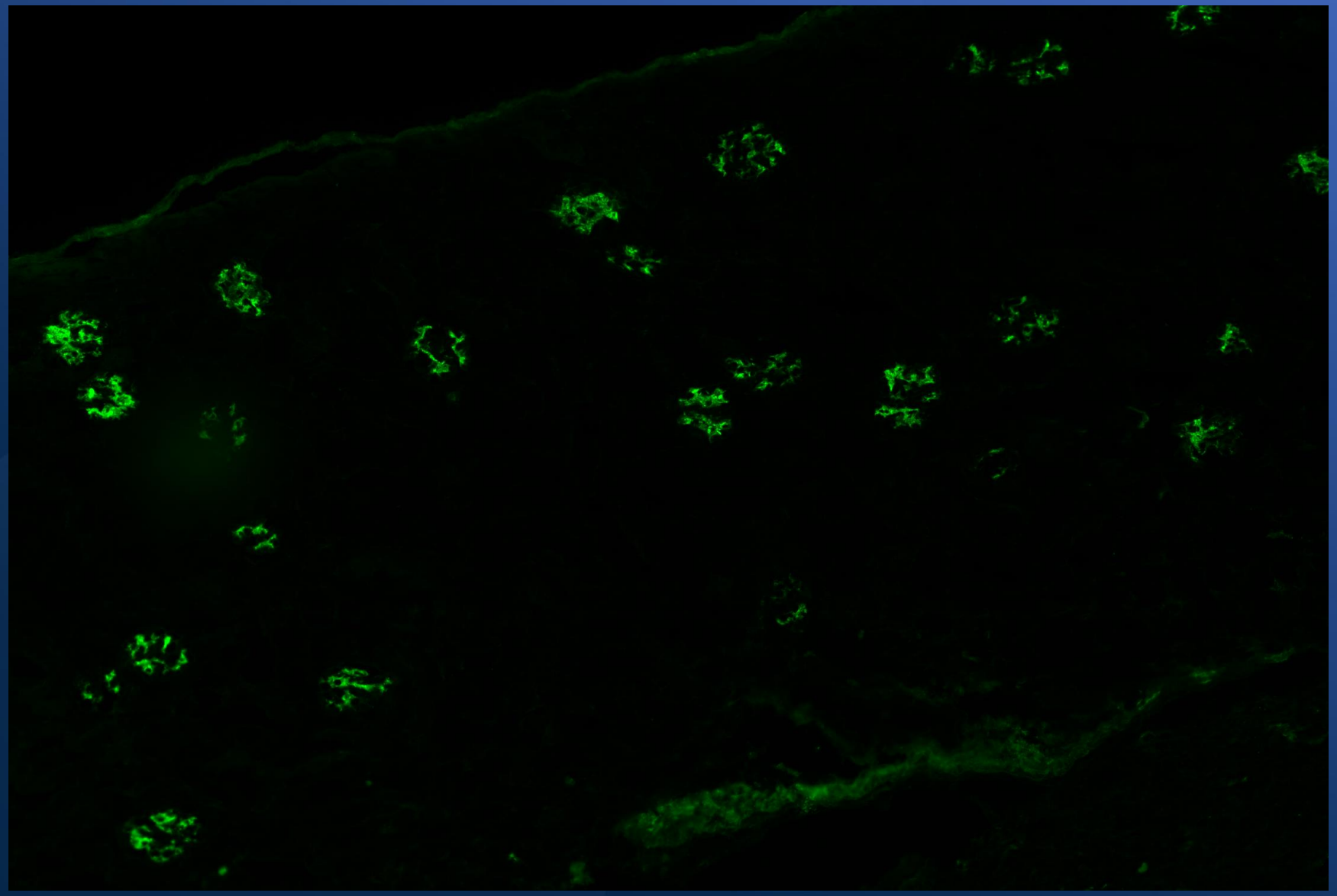


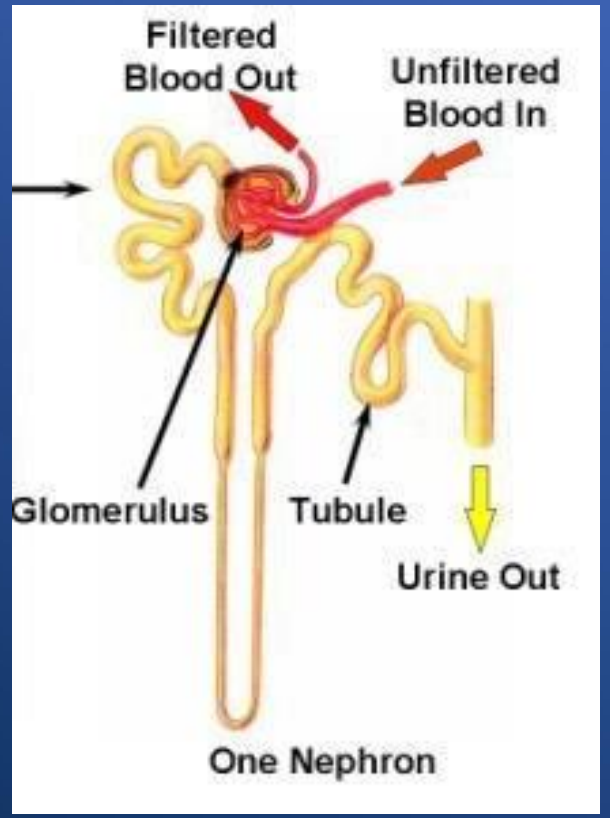




UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group





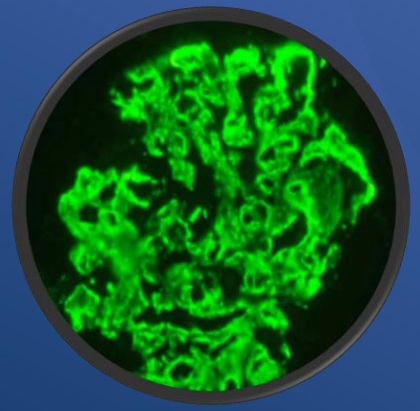
UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

Most common form of primary glomerulonephritis globally

200,000 people with IgAN in US

130,000 people with IgAN in Japan



10% of patients on dialysis have IgAN

Up to 50% of patients with IgAN develop ESKD and require dialysis

200,000 people with IgAN in EU

60% of IgAN patients with ESKD will receive ≥1 kidney transplant

800,000 people with IgAN in China

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

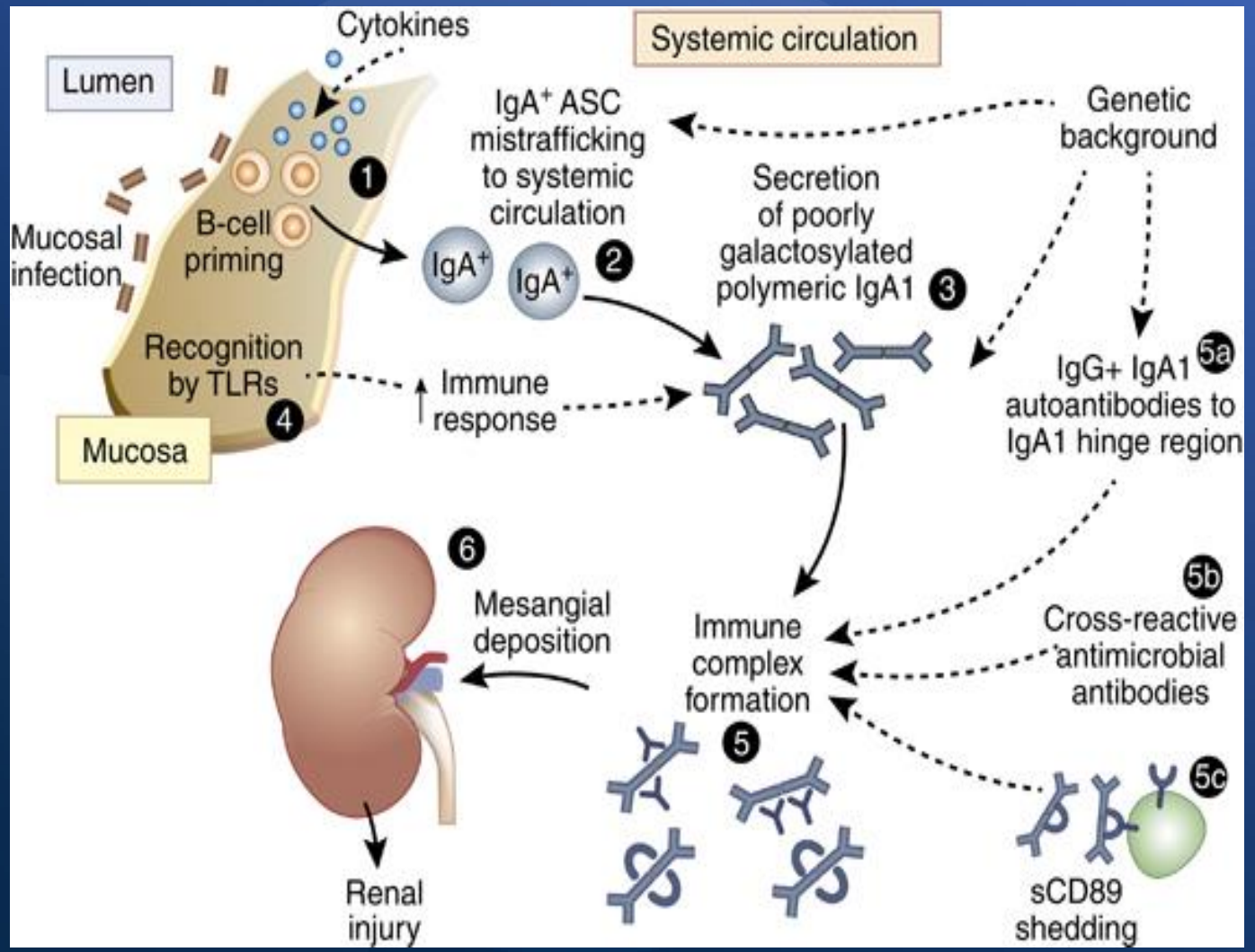
Most common form of primary glomerulonephritis globally

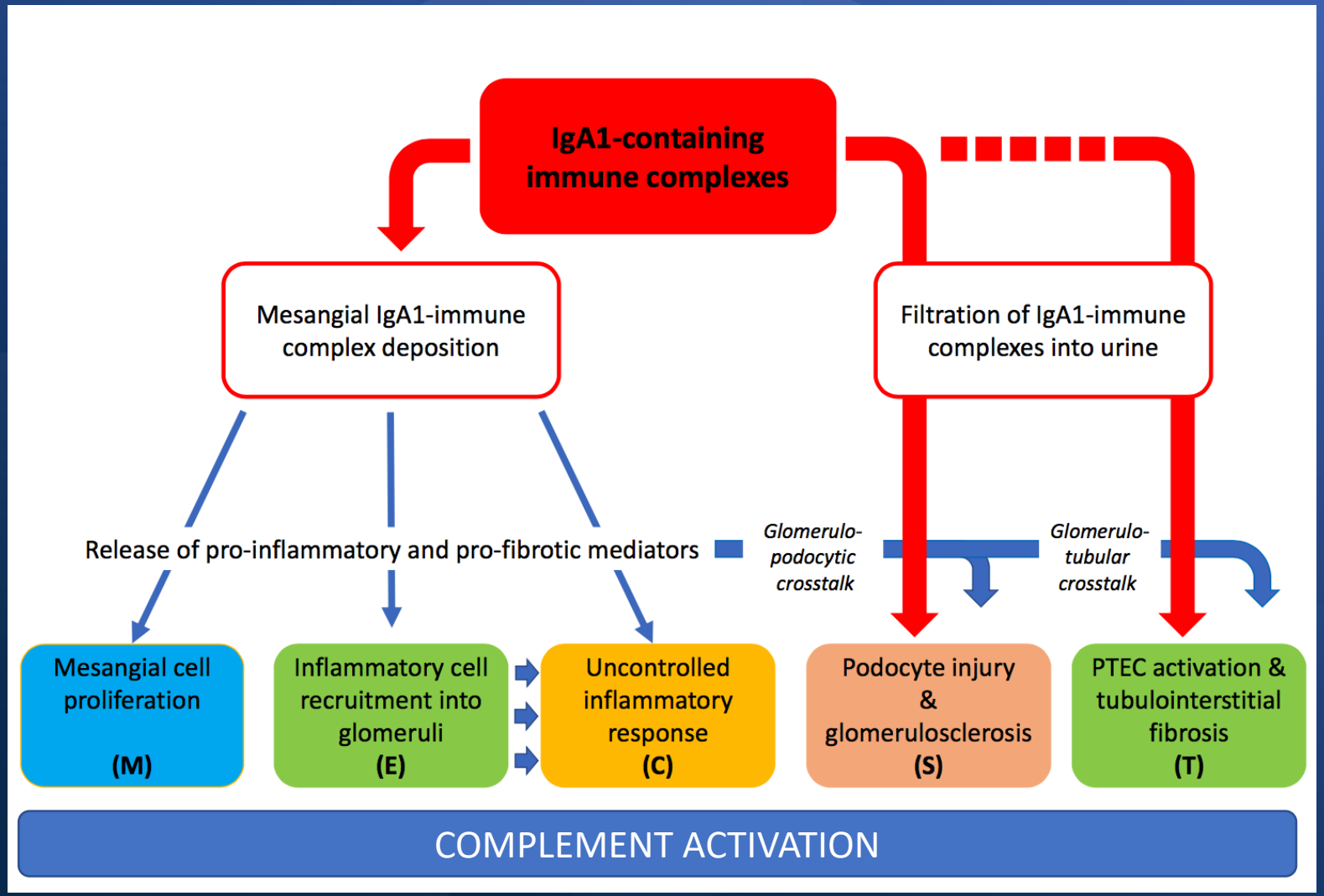
200,000 people with IgAN in US

130,000 people with IgAN in Japan

In 2022 we still have severely limited treatment options for our patients with IgA nephropathy

of IgAN patients with ESKD will receive ≥1 kidney transplant


Cytokines
Systemic circulation
Lumen
IgA+ ASC mistrafficking to systemic circulation
Genetic background
Mucosal infection
B-cell priming
1
IgA+
IgA+
2
Secretion of poorly galactosylated polymeric IgA1
3
Recognition by TLRs
4
Immune response
IgG+ IgA1 autoantibodies to IgA1 hinge region
5a
Mucosa
6
Mesangial deposition
5b
Cross-reactive antimicrobial antibodies
Immune complex formation
5
5c
sCD89 shedding
Renal injury


IgA1-containing immune complexes
Mesangial IgA1-immune complex deposition
Filtration of IgA1-immune complexes into urine
Release of pro-inflammatory and pro-fibrotic mediators
Glomerulo-podocytic crosstalk
Glomerulo-tubular crosstalk
Mesangial cell proliferation (M)
Inflammatory cell recruitment into glomeruli (E)
Uncontrolled inflammatory response (C)
Podocyte injury & glomerulosclerosis (S)
PTEC activation & tubulointerstitial fibrosis (T)
COMPLEMENT ACTIVATION

Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases

OPEN

Brad H. Rovin[1], Sharon G. Adler[2], Jonathan Barratt[3], Frank Bridoux[4], Kelly A. Burdge[5], Tak Mao Chan[6], H. Terence Cook[7], Fernando C. Fervenza[8], Keisha L. Gibson[9], Richard J. Glassock[10], David R.W. Jayne[11], Vivekanand Jha[12,13,14], Adrian Liew[15], Zhi-Hong Liu[16], Juan M. Mejía-Vilet[17], Carla M. Nester[18], Jai Radhakrishnan[19], Elizabeth M. Rave[20], Heather N. Reich[21], Pierre Ronco[22,23], Jan-Stephan F. Sanders[24], Sanjeev Sethi[25], Yusuke Suzuki[26], Sydney C.W. Tang[6], Vladimír Tesar[27], Marina Vivarelli[28], Jack F.M. Wetzels[29], Lyubov Lytvyn[30,31], Jonathan C. Craig[32,33], David J. Tunnicliffe[33,34], Martin Howell[33,34], Marcello A. Tonelli[35], Michael Cheung[36], Amy Earley[36] and Jürgen Floege[37]

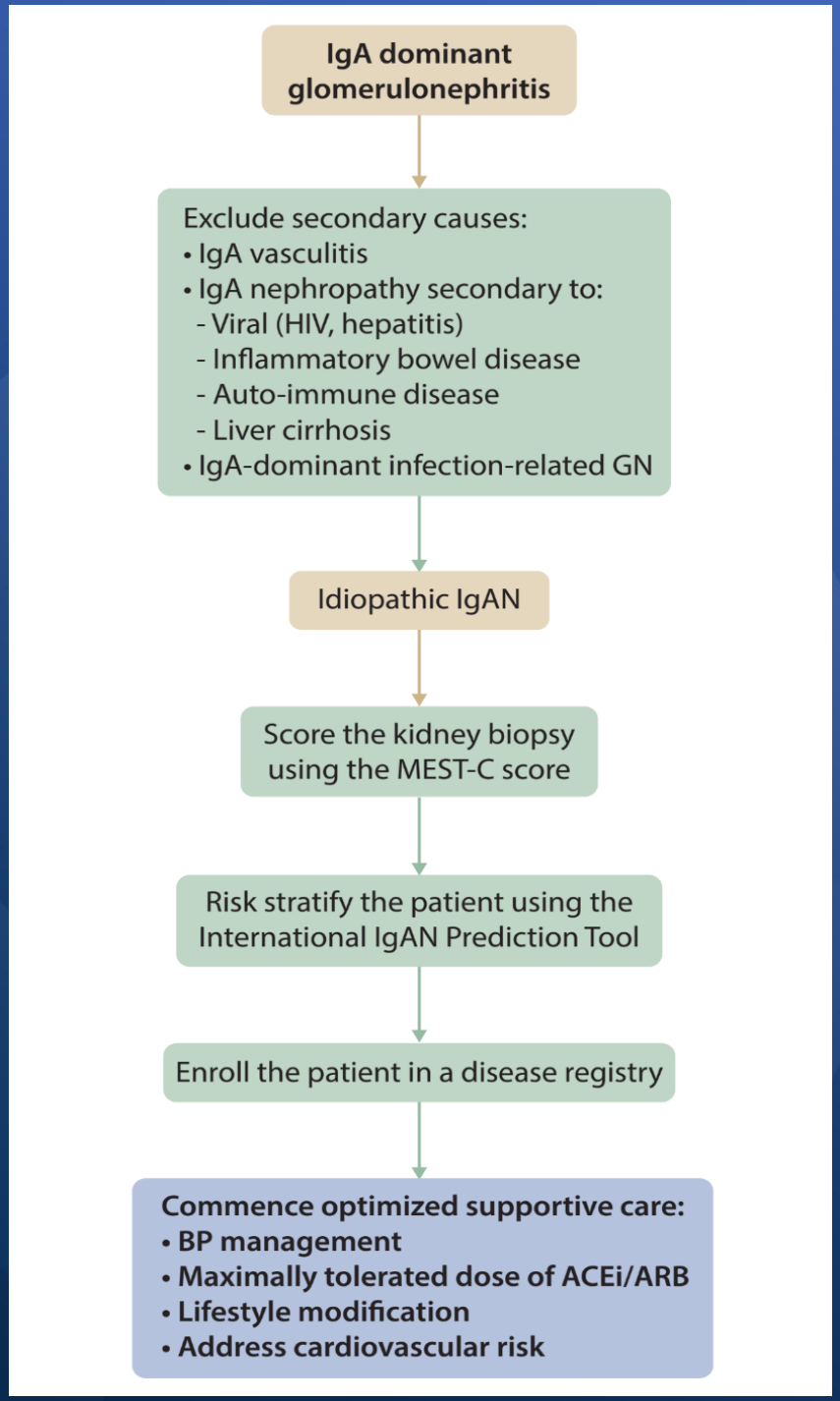
[1]Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA; [2]Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute, Los Angeles, California, USA; [3]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [4]Department of Nephrology and Renal Transplantation, CIC INSERM 1402, Centre Hospitalier Universitaire, University Hospital Poitiers, Poitiers, France; [5]Division of Nephrology, Mass General Brigham-Salem Hospital, Salem, Massachusetts, USA; [6]Division of Nephrology, Department of Medicine, University of Hong Kong, Hong Kong, China; [7]Renal and Transplant Centre, Imperial College London, London, UK; [8]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; [9]University of North Carolina Kidney Center at Chapel Hill, Chapel Hill, North Carolina, USA; [10]Department of Medicine, Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA; [11]Division of Experimental Medicine & Immunotherapeutics, School of Clinical Medicine, University of Cambridge, Cambridge, UK; [12]The George Institute for Global Health, New Delhi, India; [13]School of Public Health, Imperial College London, London, UK; [14]Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India; [15]The Kidney and Transplant Practice, Mount Elizabeth Novena Hospital, Singapore; [16]Nanjing University School of Medicine, Nanjing, China; [17]Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubiran, Mexico City, Mexico; [18]Molecular Otolaryngology & Renal Research Laboratories, University of Iowa, Iowa City, Iowa, USA; [19]Division of Nephrology, Department of Medicine, Columbia University Medical Center, New York, New York, USA; [20]Ohio Kidney Associates, Columbus, Ohio, USA; [21]Divsion of Nephrology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [22]Sorbonne University, and Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche S1155, Paris, France; [23]Le Mans Hospital, Le Mans, France; [24]Division of Nephrology, Department of Internal Medicine, University of Groningen, Groningen, The Netherlands; [25]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA; [26]Department of Nephrology, Juntendo University, Tokyo, Japan; [27]Department of Nephrology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic; [28]Department of Pediatric Subspecialties, Division of Nephrology and Dialysis, Ospedale Pediatrico Bambino Gesù, Rome, Italy; [29]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands; [30]MAGIC Evidence Ecosystem Foundation, Hamilton, Ontario, Canada; [31]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada; [32]College of Medicine and Public Health, Flinders University, Adelaide, Australia; [33]Cochrane Kidney and Transplant, Sydney, New South Wales, Australia; [34]Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia; [35]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; [36]KDIGO, Brussels, Belgium; and [37]Division of Nephrology, University Hospital, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany

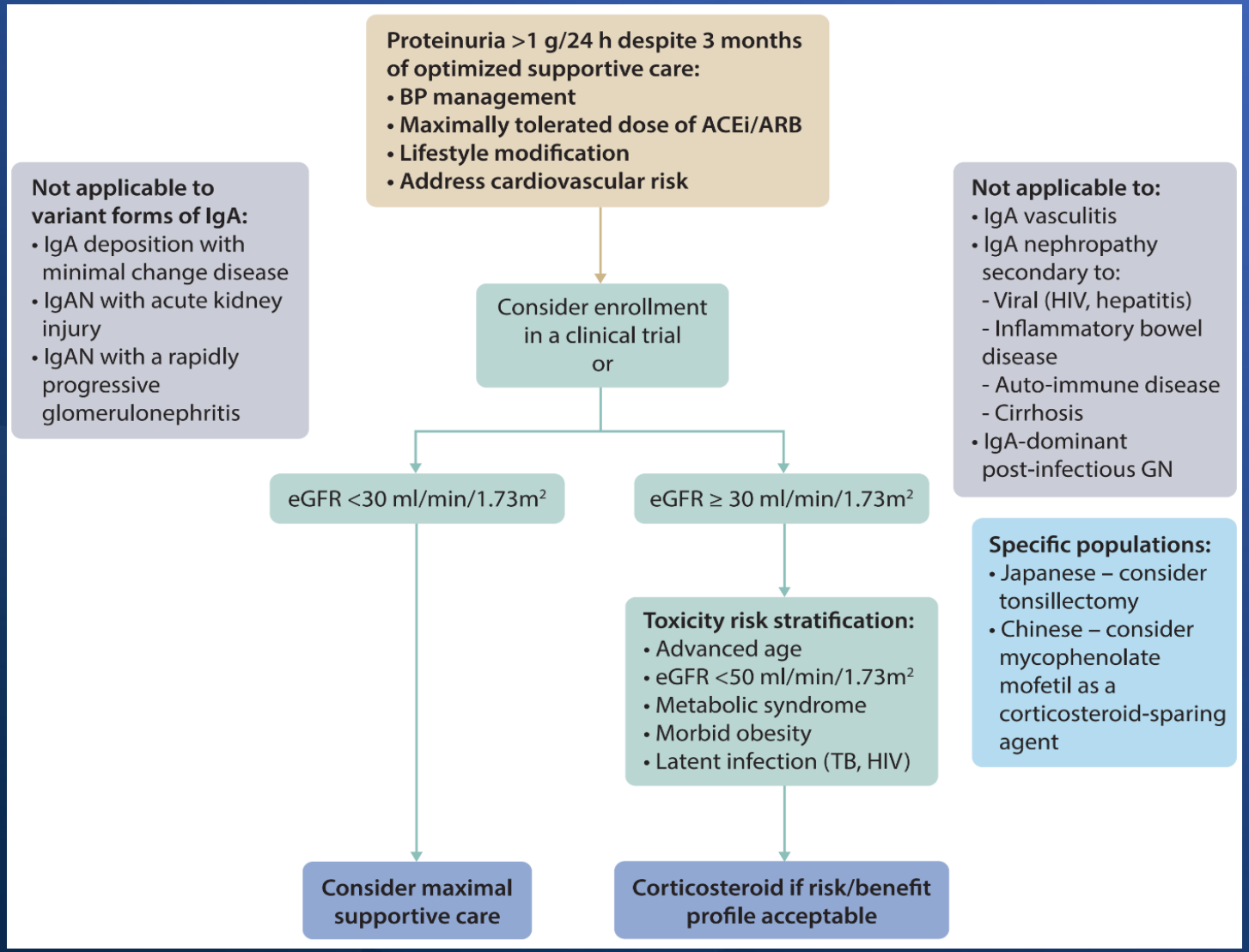
The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases is an update to the KDIGO 2012 guideline. The aim is to assist clinicians caring for individuals with glomerulonephritis (GN), both adults and children. The scope includes various glomerular diseases, including IgA nephropathy and IgA vasculitis, membranous nephropathy, nephrotic syndrome, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), infection-related GN, antineutrophil cytoplasmic antibody (ANCA) vasculitis, lupus nephritis, and anti–glomerular basement membrane antibody GN. In addition, this guideline will be the first to address the subtype of complement-mediated diseases. Each chapter follows the same format providing guidance related to diagnosis, prognosis, treatment, and special situations. The goal of the guideline is to generate a useful resource for clinicians and patients by providing actionable recommendations based on evidence syntheses, with useful infographics incorporating views from experts in the field. Another aim is to propose research recommendations for areas where

Correspondence: *Brad H. Rovin, Division of Nephrology, The Ohio State University Wexner Medical Center, 1664 Neil Avenue, Fourth Floor, Columbus, Ohio 43201, USA. E-mail: brad.rovin@osumc.edu; and Jürgen Floege, Division of Nephrology, RWTH Aachen University Hospital, Pauwelsstrasse 30, 52074 Aachen, Germany. E-mail: jfloege@ukaachen.de*

Received 14 March 2021; revised 18 May 2021; accepted 20 May 2021

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES


IgA dominant glomerulonephritis
Exclude secondary causes:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Auto-immune disease
- Liver cirrhosis
• IgA-dominant infection-related GN
Idiopathic IgAN
Score the kidney biopsy using the MEST-C score
Risk stratify the patient using the International IgAN Prediction Tool
Enroll the patient in a disease registry
Commence optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk


Proteinuria >1 g/24 h despite 3 months of optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk
Not applicable to variant forms of IgA:
• IgA deposition with minimal change disease
• IgAN with acute kidney injury
• IgAN with a rapidly progressive glomerulonephritis
Consider enrollment in a clinical trial or
eGFR <30 ml/min/1.73m²
eGFR ≥ 30 ml/min/1.73m²
Not applicable to:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Auto-immune disease
- Cirrhosis
• IgA-dominant post-infectious GN
Specific populations:
• Japanese – consider tonsillectomy
• Chinese – consider mycophenolate mofetil as a corticosteroid-sparing agent
Toxicity risk stratification:
• Advanced age
• eGFR <50 ml/min/1.73m²
• Metabolic syndrome
• Morbid obesity
• Latent infection (TB, HIV)
Consider maximal supportive care
Corticosteroid if risk/benefit profile acceptable

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

Doing Our Part 6ft NATIONAL KIDNEY FOUNDATION®

Login Donate

Kidney Basics | Treatment & Support | Kidney Donation | Kidney Professionals | Research | Get Involved

National Kidney Foundation's and IgA Nephropathy Foundation's Externally-Led Patient-Focused Drug Development (EL-PFDD) Meeting on IgA Nephropathy

On August 19, 2019, the National Kidney Foundation and the IGA Nephropathy Foundation of America held an EL-PFDD Meeting on IgA nephropathy.

You can:

- **Read the Voice of the Patient Report (the meeting report) here**
- **Listen to the meeting recording here**
- **Read the meeting transcript here**
- **Learn more about the meeting from the pre-meeting webpage below.**

About EL-PFDD Meetings

Externally-led Patient-focused Drug Development (EL-PFDD) meetings bring together patients and their care-partners, representatives from the US Food and Drug Administration (FDA), pharmaceutical companies interested in developing drugs for the disease, and doctors who are experts in the particular disease- all to hear from patients about the disease in question. In these meetings, the patient's experience is brought to the forefront for the FDA and pharmaceutical companies to understand. "Externally-led" refers to PFDD meetings that are led by organizations outside of the FDA.

EL-PFDD meetings benefit four groups of stakeholders:

- **FDA in its role to approve new medicines**
  - EL-PFDD meetings help the FDA to understand what it's like to live with a particular disease, and therefore, what symptoms and burdens matter most to patients.
  - These meetings also inform the FDA on what side effects patients may be willing to accept to gain a certain level of symptom relief or slowing of their disease progression.
  - EL-PFDD meetings reveal to the FDA what patients need regarding new drugs, and what their preferences are for clinical trials for their disease.
  - Such knowledge helps the FDA determine whether a potential drug's risks or limitations will be worth it's benefits to patients, and how closely it will meet patients' needs.
  - EL-PFDD meetings can support making medicines available to patients by helping to identify areas of unmet need in the patient population.

Doing Our Part 6ft NATIONAL KIDNEY FOUNDATION®

Login

Kidney Basics | Treatment & Support | Kidney Donation | Kidney Professionals | Re

Hundreds of IgA Nephropathy Patients Share Experience with FDA, Professionals, Drug-makers

The National Kidney Foundation presents "Voice of the Patient Report: IgA Nephropathy" to federal agency

Dec. 8, 2020, New York, NY —The National Kidney Foundation (NKF) in partnership with the IGA Nephropathy Foundation of America, Inc. (IGANF), submitted the "Voice of the Patient Report: IgA Nephropathy" to the U.S Food and Drug Administration (FDA) today.

In August 2019, NKF and IGANF gathered, in person and virtually, hundreds of patients and their caregivers to share their first-hand experiences with IgA nephropathy, a disease that can lead to kidney failure. The subsequent report is presented to the FDA and will be used as the federal agency considers approval applications for future drug treatments and clinical trials. Healthcare professionals and drug-makers will also receive the report to learn more about patients' concerns and experiences with the disease.

IgA nephropathy, formerly Berger's disease, is called IgAN for short. It is a condition that damages the filters (glomeruli) inside the kidneys, causing the kidneys to lose function. IgAN is a slowly progressing disease. Glomerular diseases include many conditions with many different causes.

"We are grateful to the patients and their caregivers who raised their voices and courageously spoke openly about their daily journey with IgAN," said NKF's Chief Executive Officer Kevin Longino and a kidney transplant patient. "This is our fifth 'Voice of Patient Report' on a disease that affects the kidneys, and we are committed to doing more in the future. It is important that we create opportunity for patients and their care partners to speak directly to those who control the levers of policy, drug development, and medical care."

IgAN is considered a rare disease, but it is estimated that about 60,000 in the U.S. have the illness. There ae no FDA-approved treatments for IgAN. It is treated supportively with corticosteroids (often called "steroids"), immunosuppressive drugs, blood pressure medications called ACE inhibitors and ARBs, salt restriction if the body retains extra fluid.

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

KEY THEMES FROM PATIENTS' VOICES

Throughout the day's activities, the voices of IgAN patients conveyed clearly the following key messages:

- Patients with IgAN continuously deal with very difficult issues in their daily lives. The symptoms that most negatively affect daily life include:
    - Being tired, exhausted or fatigued
    - Experiencing "brain fog"
    - Anxiety and/or depression
    - High blood pressure
    - Gastrointestinal problems
    - Swelling (e.g., ankles, face, etc.)
- Emotional and social difficulties commonly accompany IgAN, and are attributed to these key factors:
    - Others don't know what it's like to live with IgAN
    - General daily function is limited
    - Social isolation
    - Family stress
    - Difficulty with relationships outside of family
    - Uncertainty and unpredictability of the disease
- Disease symptoms and side effects from medications prevent patients with IgAN from engaging in the activities that are important to them and that they enjoy, including:
    - Participation in sports or other physical activities
    - Attendance at work or school
    - Going outdoors (aversion because of heat or cold intolerance)
    - Participating in social activities

- Many patients are willing to participate in clinical trials, particularly if the side effects are limited, but a high percentage have been unaware or are not eligible for trials:
    - Patients feel that eligibility for clinical trials needs to be expanded to include pediatric patients.
    - Patients feel that eligibility for clinical trials needs to be expanded to include patients who have had a kidney transplant.
    - The requirement for more than one kidney biopsy in a year significantly reduces the willingness of patients to participate in a clinical trial.
- Patients expressed a willingness to participate in clinical trials conducted under an Accelerated Approval Program and to remain in such trials for the long-term, even after the drug is continuing to be studied is approved and marketed:
    - Majority of patients voiced a high tolerance for risk, and a commitment to remaining in clinical trials for one, two, and even three years after a drug is on the market, even if they had to remain in a placebo arm.
- There are currently no FDA-approved therapies that target the disease-specific mechanism of IgAN, or that significantly reduce progression towards end-stage kidney disease:
    - Treatments focus on managing high blood pressure and reducing inflammation
    - Angiotensin converting enzyme inhibitors and receptor blockers are the cornerstones for medical treatment for IgAN; they are not curative
    - Thirteen percent of patients polled believe their current treatments do not work at all, and only 14% responded that their treatments work “very well”
    - Patients reported managing their IgAN in part by lifestyle changes focused on diet (e.g., limitations on salt and protein) and exercise (e.g., yoga)
- The side effects of corticosteroid treatments, such as prednisone, are long-lasting and have a strong impact on IgAN patients, the most serious and life-altering effects include:
    - Weight gain and swelling (edema)
    - Muscle, bone, and joint damage
    - Irritability, moodiness, and aggressiveness

- Patients would be very confident in their decision to take a new medicine that has been approved based on evidence from clinical measures including:
    - Reduced proteinuria
    - Slowing the rate of loss of kidney function
    - Improvements in how they would feel, function and/or survive
- Overwhelmingly, IgAN patients desire a new treatment option that will halt the progression of disease or delay the need for dialysis:
    - Enthusiasm for such a treatment is significantly reduced if the side effect profile is more severe than current medications.

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

RESEARCH RECOMMENDATIONS

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

❖ **Evaluation of therapeutic strategies that minimize or avoid systemic corticosteroid exposure:**

Emerging data are required to clarify the role of novel therapies in **non-immunosuppressive comprehensive supportive care**.

- Endothelin Receptor Antagonism: **sparsentan (PROTECT) & atrasentan (ALIGN)**
- SGLT2 inhibition: **DAPA CKD** (kidney and cardiovascular outcomes in non-diabetic kidney disease)

KDIGO Kidney Disease Improving Global Outcomes

RESEARCH RECOMMENDATIONS

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

❖ **Evaluation of therapeutic strategies that minimize or avoid systemic corticosteroid exposure:**

- Targeted-release formulation (TRF) of budesonide
- Inhibition of B cell activation and survival
- Inhibition of the complement system

UNIVERSITY OF LEICESTER

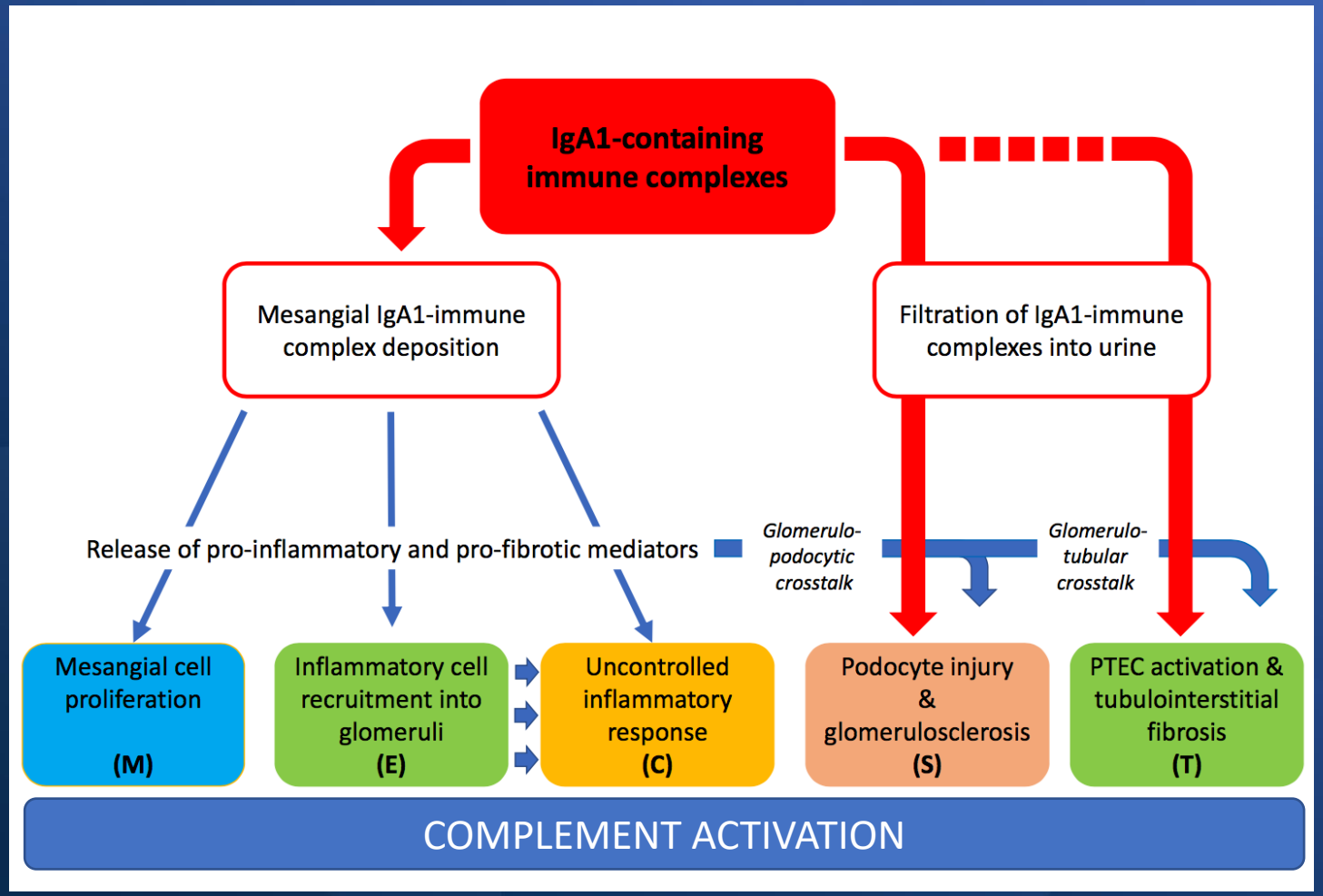
Leicester IgA Nephropathy Research Group

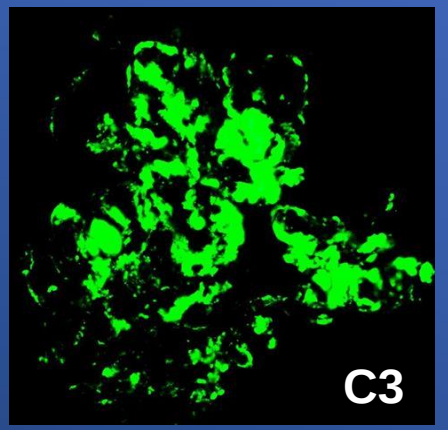
Phase 3 studies in 2022-Recruiting and in Follow-Up

Trial	Agent	MoA	Primary Interim Endpoint*
NEFIGARD	Nefecon (targeted-release budesonide)	Corticosteriod (targeted release in the distal ileum)	Change in UP/C from baseline to 9 months
PROTECT	Sparsentan	DEARA (Dual Endothelin Angiotensin Receptor Antagonist)	Change in UP/C from baseline to Week 36
ALIGN	Atrasentan	ET_AR antagonist	Change in UP/C from baseline to Week 24
APPLAUSE-IgAN	Iptacopan	Factor B inhibitor (alternative complement pathway)	Ratio to baseline in UP/C at 9 months
ARTEMIS-IGAN	Narsoplimab	MASP-2 inhibitor (lectin complement pathway)	Change in 24-hour UPE from baseline to Week 36
VISIONARY	Sibeprenlimab	APRIL inhibitor	Change in UPCR from a 24-hour collection from baseline to Week 36

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group





PAPERS AND ORIGINALS

Isolated Glomerulonephritis with Mesangial IgA Deposits

J. G. P. SISSONS, D. F. WOODROW, J. R. CURTIS, D. J. EVANS, P. E. GOWER, J. C. SLOPER, D. K. PETERS

British Medical Journal, 1975, 3, 611-614

Summary

Mesangial deposits of IgA, occurring in the absence of systemic disease known to be associated with nephritis, were detected by immunofluorescence microscopy in renal biopsy specimens from 25 patients (4% of 630 specimens studied). Associated deposits of C3 were always present, usually with IgG, but IgM deposits were less common and C1q was never seen. On light microscopy most of the biopsy specimens showed mesangial or focal nuclear proliferation though some were normal.

Fifteen of the 25 patients presented with macroscopic haematuria, which was usually recurrent and preceded by a sore throat, whereas the remaining, and usually older, patients presented with persistent proteinuria and were more likely to have impaired renal function.

This incidence of "mesangial IgA disease" is less than that reported by French workers. There was a significantly high incidence of familial renal disease among these patients. No abnormalities of serum complement or IgA concentration were found.

Introduction

Immunofluorescent staining of renal biopsy specimens from patients with glomerulonephritis shows depostis of immunoglobulin and complement in most cases (except in patients with steroid-sensitive nephrotic syndrome). Usually the deposits are of IgG and C3, sometimes with IgM. Deposits of IgA are seen less commonly but are found within the capillary wall in the nephritis of systemic lupus erythematosus[1] and less frequently in other types of proliferative, and occasionally membranous, nephritis.[2]

Berger first drew attention to the association between IgA deposits in the mesangium (often with accompanying deposits of IgG and C3) and "idiopathic" focal proliferative nephritis and the clinical syndrome of recurrent macroscopic haematuria[1,3]; mesangial IgA deposits are also usually found in the nephritis of Henoch-Schönlein purpura.[1] Mesangial IgA deposits have since been reported as the commonest immunofluorescent finding accompanying "idiopathic" focal proliferative glomerulonephritis in two other large French series.[4,5] The terms "Berger's disease" and "mesangial IgA disease" are often applied to this condition, though it is not yet clear whether it is a single disease entity.[6]

Mesangial IgA deposits are less common in our experience than in the French series, occurring in only about 4% of renal biopsy specimens studied by immunofluorescence over four years. We describe here the characteristics of 25 patients with glomerular mesangial IgA deposits without systemic disease and discuss whether they suffer from a distinctive disease entity.

Patients

Immunofluorescence showed that 16 out of 400 specimens obtained for biopsy at Hammersmith Hospital in 1970-4 and nine out of 230 biopsy specimens obtained at Charing Cross Hospital in 1971-4 had IgA deposits, though the patients from whom the specimens were taken had no systemic disease (patients with Henoch-Schönlein purpura were excluded from this study). All except two of these patients were followed since renal biopsy. Clinical details of the 25 patients are shown in table I. Fifteen patients (cases 1-15) were mostly young men who presented with painless macroscopic haematuria, which was recurrent in all but three cases. The episodes of haematuria usually lasted one to three days, and were preceded in all but one patient (case 14) by sore throat and malaise for 24-48 hours; in three patients heavy exercise seemed to precipitate haematuria. One patient (case 14) had persistent macroscopic haematuria for one month and his renal function deteriorated rapidly over one year. Proteinuria was not heavy in these patients, and renal function remained normal

Hammersmith Hospital and Royal Postgraduate Medical School, London W12 0HS
J. G. P. SISSONS, M.B., M.R.C.P., Assistant Lecturer in Medicine
D. K. PETERS, M.B., F.R.C.P., Reader in Medicine
D. J. EVANS, M.B., M.R.C.PATH., Reader in Pathology

Charing Cross Hospital Medical School, London W6
D. F. WOODROW, PH.D., M.B., Lecturer in Experimental Pathology
J. R. CURTIS, M.D., F.R.C.P., Consultant Nephrologist
P. E. GOWER, M.D., M.R.C.P., Consultant Nephrologist
J. C. SLOPER, M.D., F.R.C.PATH., Professor of Experimental Pathology

IgA Nephropathy

Ralph C. McCoy, MD, Carlos R. Abramowsky, MD and C. Craig Tisher, MD

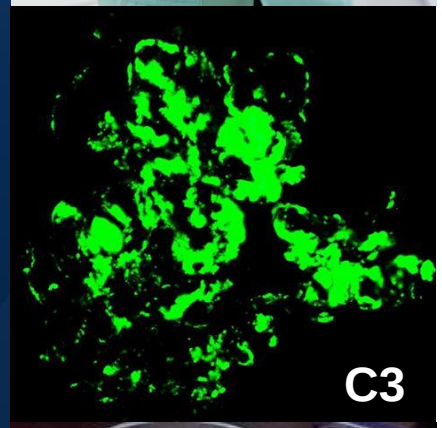
From a series of 470 specimens of renal tissue examined by immunofluorescence microscopy, 20 specimens were identified and studied in detail from patients without evidence of systemic disease in which IgA was the predominant localizing immunoglobulin. All patients presented with hematuria which was recurrent or persistent, often being exacerbated by upper respiratory infection. Most of the group pursued a benign clinical course with little evidence of decline in renal function. Histopathologic changes in renal biopsy specimens of most of the group consisted of a proliferative glomerulonephritis of variable intensity. Characteristic alterations were seen by electron microscopy which included the presence of electron-dense deposits within the mesangium, the hilar regions of the glomerulus and the basement membrane of Bowman's capsule. Evidence for activation of complement by the alternate pathway at C3 was found with properdin localization in 14 of 15 specimens and with the absence of detectable C1q and C4 in 15 specimens studied for these early acting components. It is concluded that the combined clinical, morphologic and immunologic findings warrant consideration of IgA nephropathy as a distinct clinicopathologic entity (Am J Pathol 76:123–144, 1974).

In 1968, BERGER [1,2] described a nephropathy characterized by glomerular mesangial localization of IgA with less intense localization of IgG and β1C-globulin in patients with no evidence of systemic disease such as lupus erythematosus or anaphylactoid purpura. Most of these patients had normal renal function with gross or microscopic hematuria and light proteinuria which was frequently exacerbated by upper respiratory infection. Histologically, the patients most commonly exhibited a focal glomerulonephritis. Since the initial reports by Berger,[1,2] opinion has varied among investigators regarding the nature of this clinicopathologic entity. McEnery *et al* [3] described IgA, IgG and β1C-globulin localization without IgM localization in glomeruli of 9 patients who were clinically similar to those described by Berger. Lowance *et al*,[4] on the other hand, described a group of 15 patients in which IgA was the predominant immunoglobulin present within the glomerular

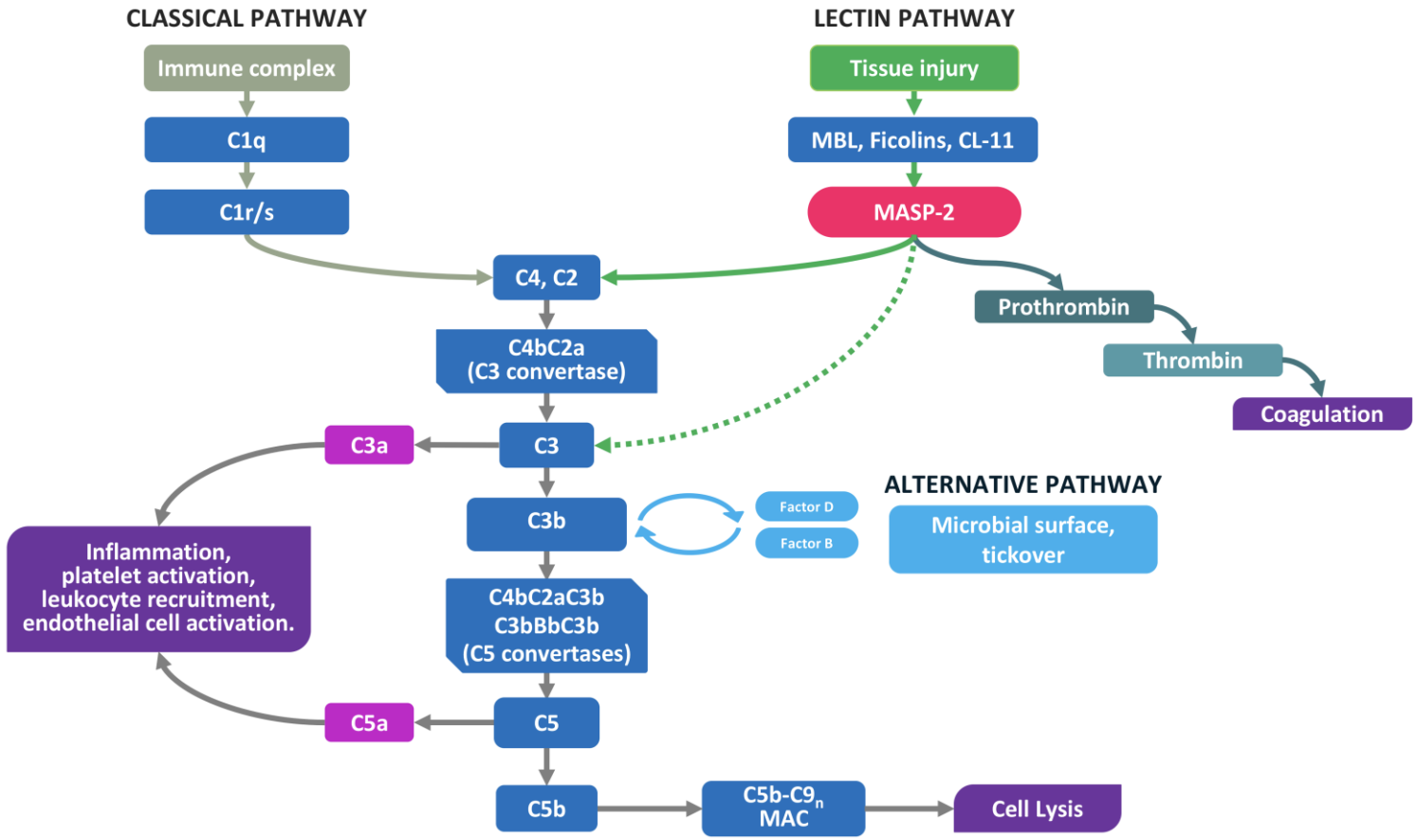
From the Department of Pathology and the Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, NC.
Supported in part by Grants AM-13084 and AM-13845 from the US Public Health Service; Dr. Tisher is the recipient of Research Career Development Award HL-440074 from the US Public Health Service.
Accepted for publication March 4, 1974.
Address reprint requests to Dr. Ralph C. McCoy, Department of Pathology, Box 3712, Duke University Medical Center, Durham, NC 27710.

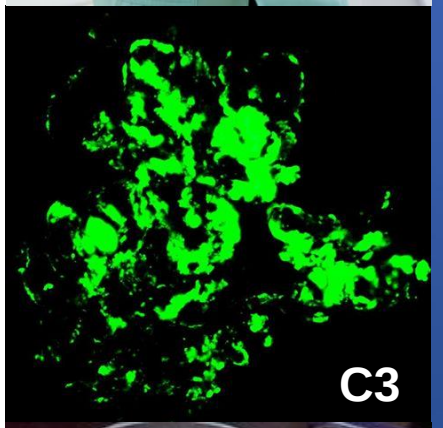
UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

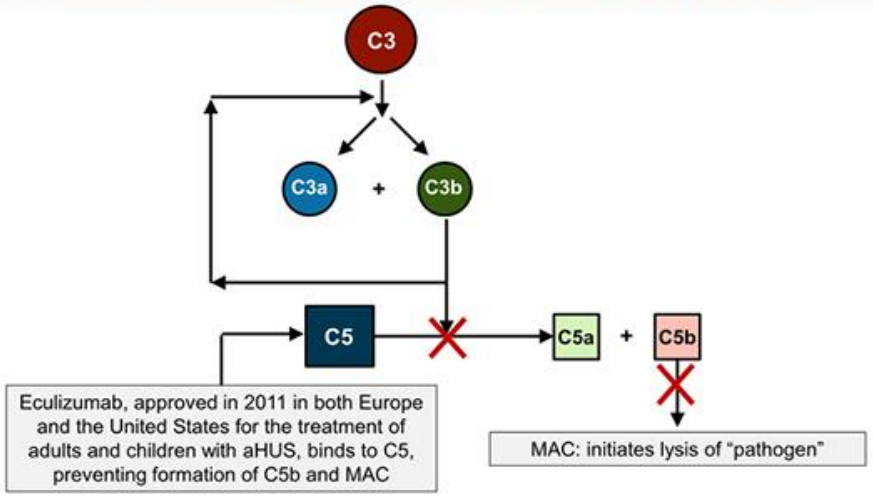


PATHWAYS OF COMPLEMENT ACTIVATION





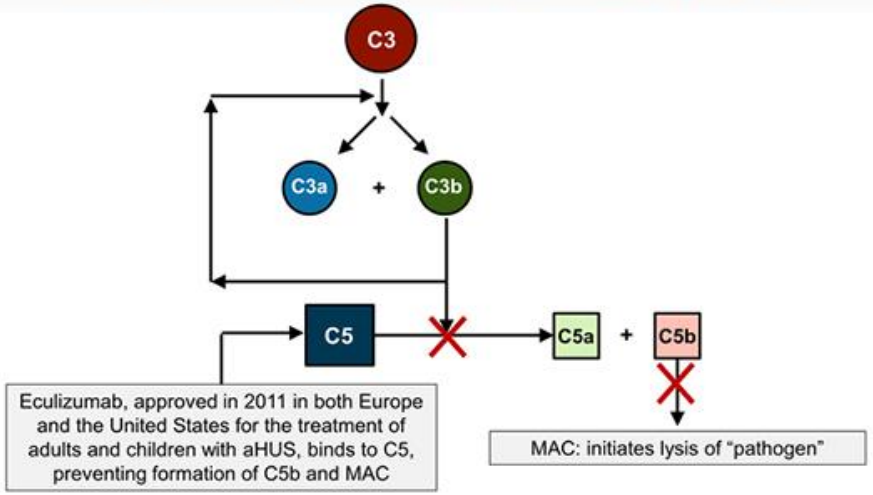
Eculizumab
A Monoclonal, Humanized Antibody to C5



UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

Eculizumab
A Monoclonal, Humanized Antibody to C5



Clinical Kidney Journal

ckj OXFORD

Clinical Kidney Journal, 2015, vol. 8, no. 5, 489–491
doi: 10.1093/ckj/sfv076
Advance Access Publication Date: 27 August 2015
Exceptional Case

EXCEPTIONAL CASE

Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum?

Troels Ring[1], Birgitte Bang Pedersen[1], Giedrius Salkus[2], and Timothy H.J. Goodship[3]

[1]Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark, [2]Department of Pathology, Aalborg University Hospital, Aalborg, Denmark, and [3]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

Pediatr Nephrol (2014) 29:2225–2228
DOI 10.1007/s00467-014-2863-y

BRIEF REPORT

Eculizumab treatment for rescue of renal function in IgA nephropathy

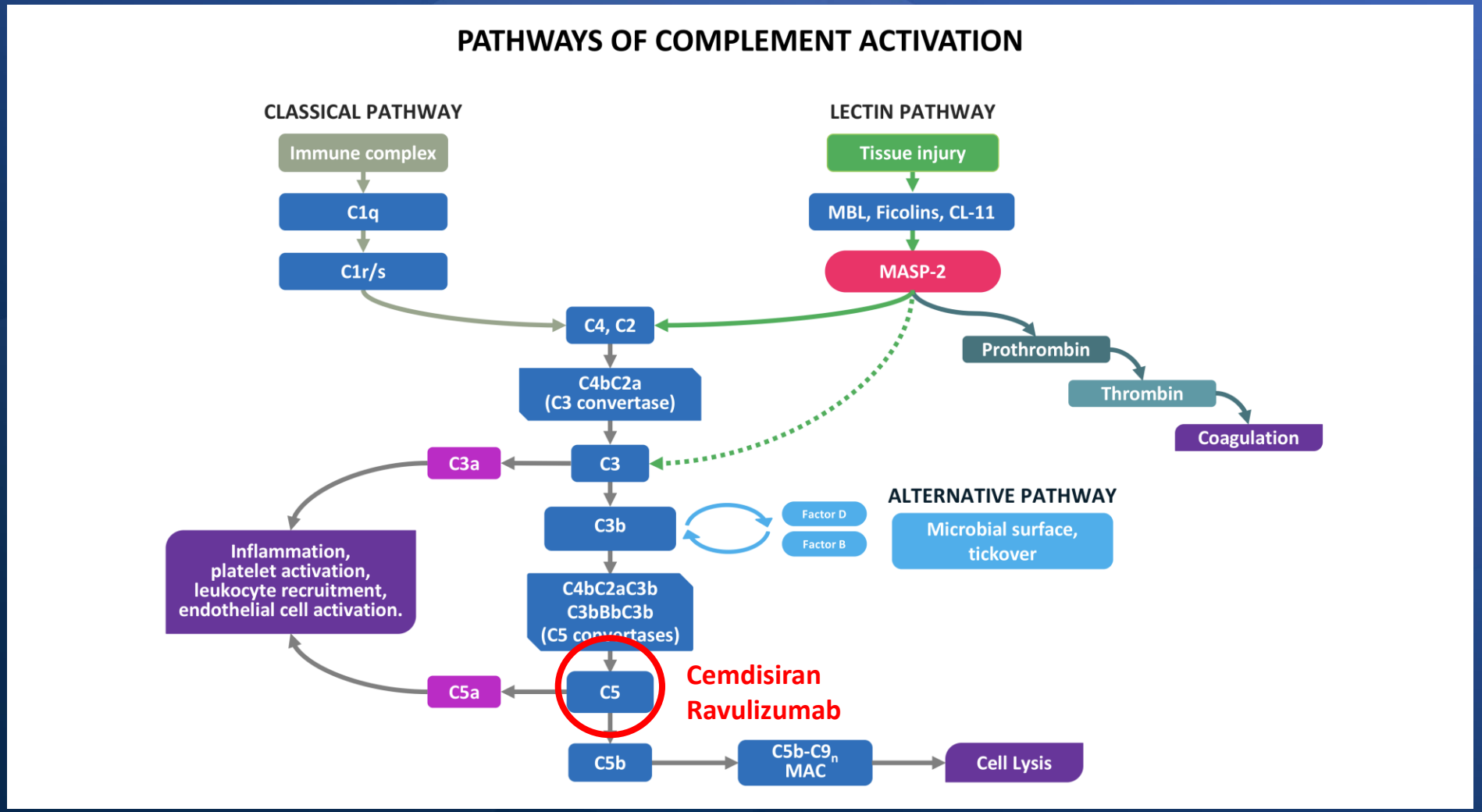
Therese Rosenblad · Johan Rebetz · Martin Johansson · Zivile Békássy · Lisa Sartz · Diana Karpman

ELSEVIER CrossMark

First Treatment of Relapsing Rapidly Progressive IgA Nephropathy With Eculizumab After Living Kidney Donation: A Case Report

A.L. Herzog[a,*], C. Wanner[a], K. Amann[b], and K. Lopau[a]

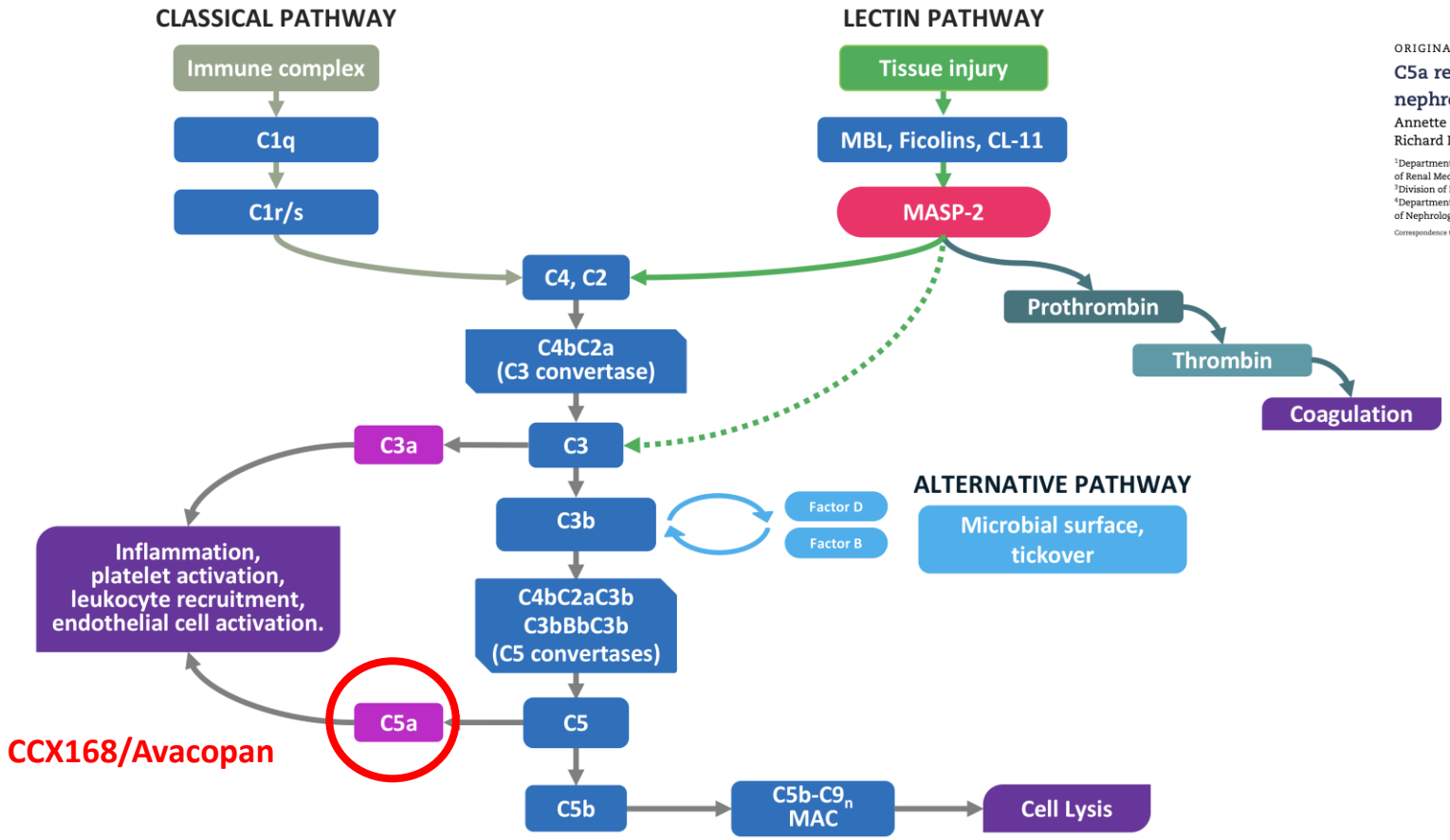
[a]Division of Nephrology, Medizinische Klinik I, Transplantationszentrum, University of Würzburg, Universitätsklinikum, Würzburg, Germany; and [b]Department of Nephropathology, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

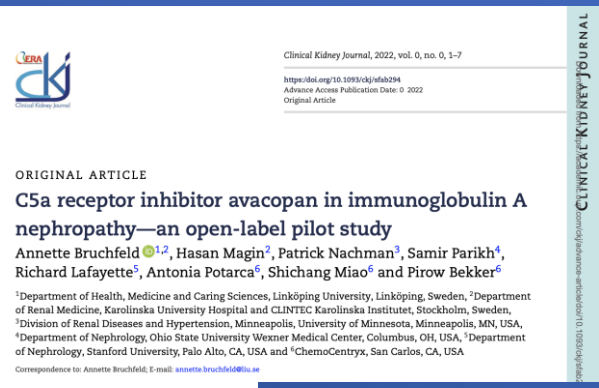

PATHWAYS OF COMPLEMENT ACTIVATION
CLASSICAL PATHWAY
Immune complex
C1q
C1r/s
LECTIN PATHWAY
Tissue injury
MBL, Ficolins, CL-11
MASP-2
C4, C2
C4bC2a
(C3 convertase)
Prothrombin
Thrombin
Coagulation
C3a
C3
ALTERNATIVE PATHWAY
Microbial surface,
tickover
Factor D
Factor B
C3b
Inflammation,
platelet activation,
leukocyte recruitment,
endothelial cell activation.
C4bC2aC3b
C3bBbC3b
(C5 convertases)
C5a
C5
Cemdisiran
Ravulizumab
C5b
C5b-C9n
MAC
Cell Lysis

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

PATHWAYS OF COMPLEMENT ACTIVATION





Clinical Kidney Journal, 2022, vol. 0, no. 0, 1–7

https://doi.org/10.1093/ckj/sfab294
Advance Access Publication Date: 0 2022
Original Article

ORIGINAL ARTICLE

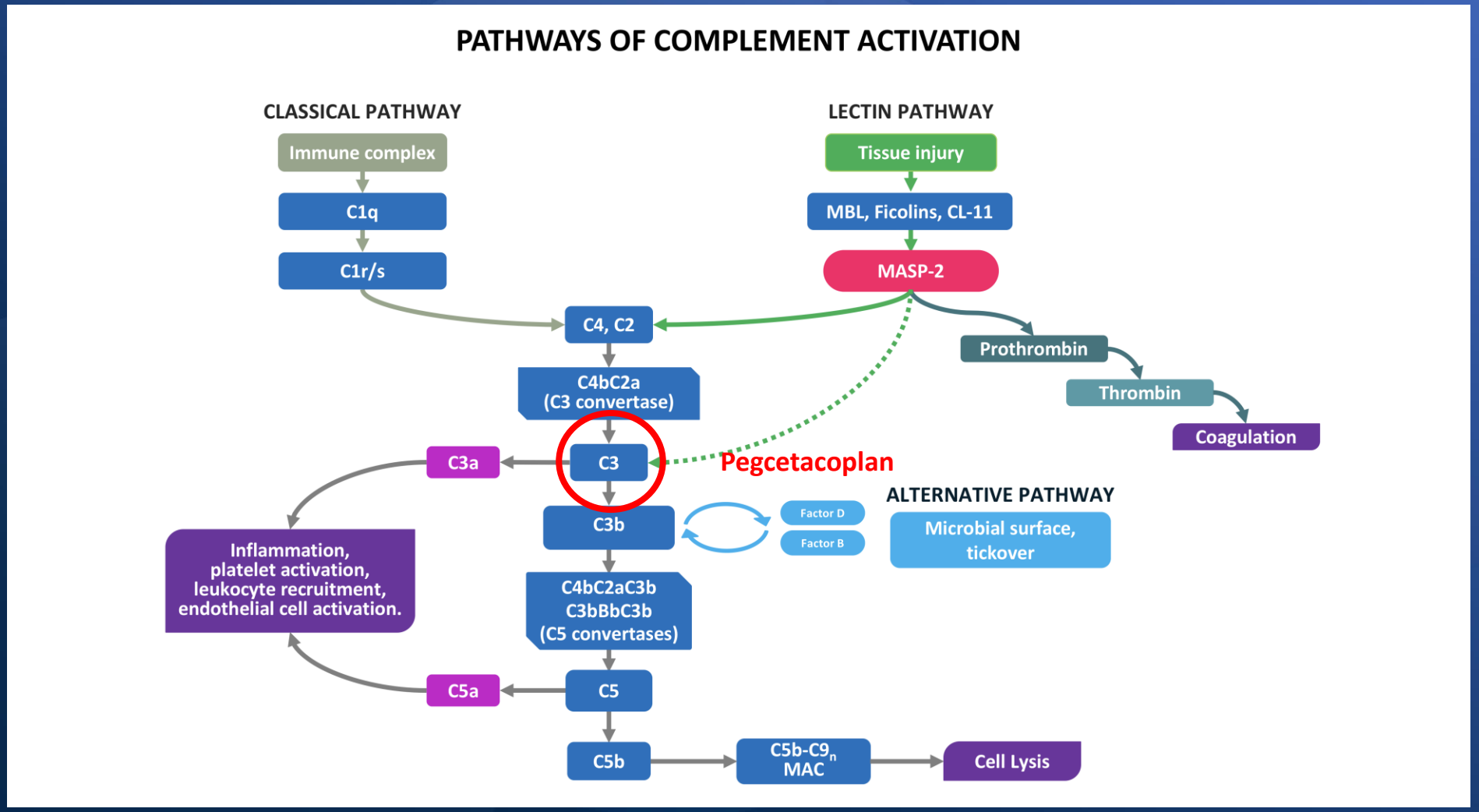
C5a receptor inhibitor avacopan in immunoglobulin A nephropathy—an open-label pilot study

Annette Bruchfeld[1,2], Hasan Magin[2], Patrick Nachman[3], Samir Parikh[4], Richard Lafayette[5], Antonia Potarca[6], Shichang Miao[6] and Pirow Bekker[6]

[1]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, [2]Department of Renal Medicine, Karolinska University Hospital and CLINTEC Karolinska Institutet, Stockholm, Sweden, [3]Division of Renal Diseases and Hypertension, Minneapolis, University of Minnesota, Minneapolis, MN, USA, [4]Department of Nephrology, Ohio State University Wexner Medical Center, Columbus, OH, USA, [5]Department of Nephrology, Stanford University, Palo Alto, CA, USA and [6]ChemoCentryx, San Carlos, CA, USA

Correspondence to: Annette Bruchfeld; E-mail: annette.bruchfeld@liu.se

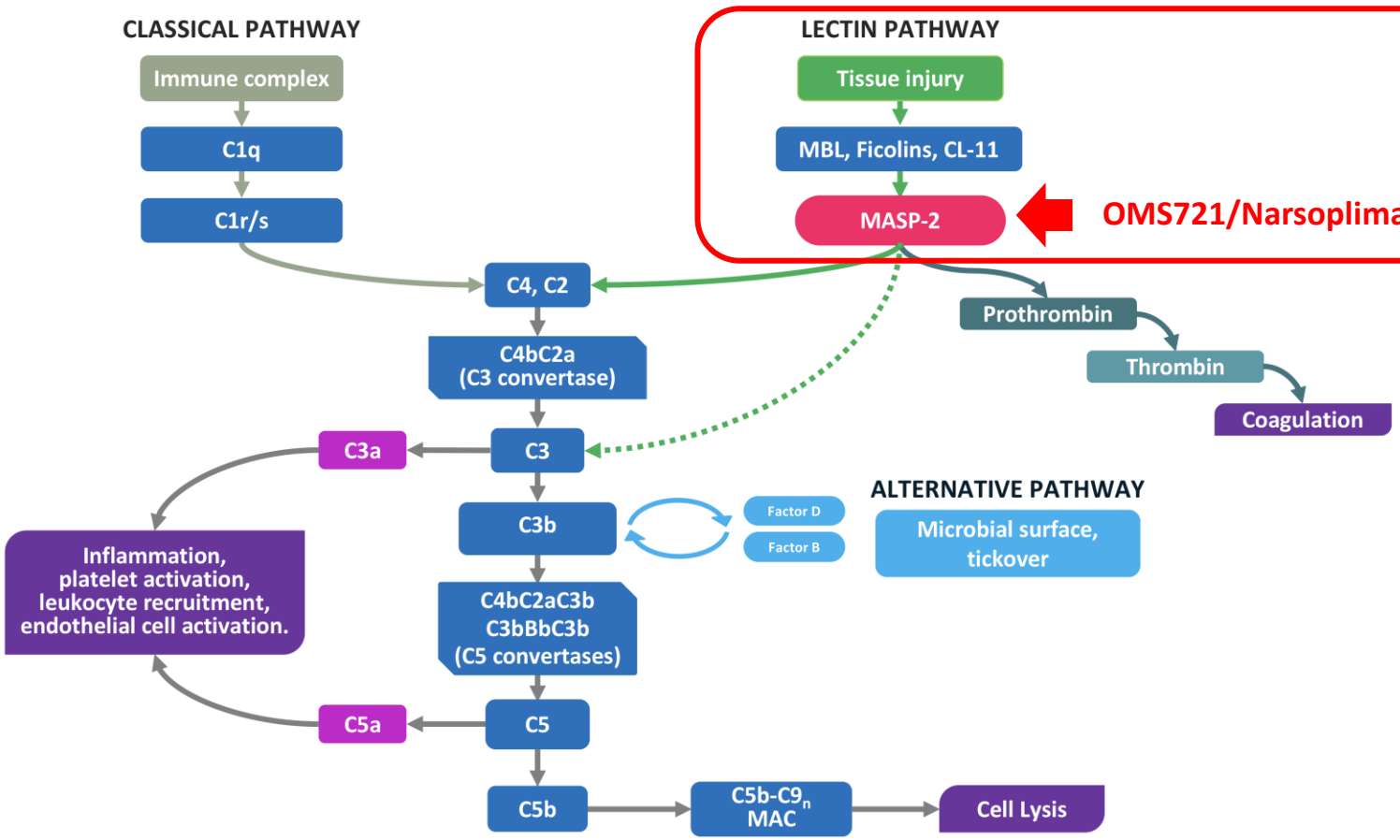
CLINICAL KIDNEY JOURNAL


PATHWAYS OF COMPLEMENT ACTIVATION
CLASSICAL PATHWAY
Immune complex
C1q
C1r/s
LECTIN PATHWAY
Tissue injury
MBL, Ficolins, CL-11
MASP-2
C4, C2
C4bC2a
(C3 convertase)
Prothrombin
Thrombin
Coagulation
C3a
C3
Pegcetacoplan
ALTERNATIVE PATHWAY
Factor D
Factor B
C3b
Microbial surface,
tickover
Inflammation,
platelet activation,
leukocyte recruitment,
endothelial cell activation.
C4bC2aC3b
C3bBbC3b
(C5 convertases)
C5a
C5
C5b
C5b-C9n
MAC
Cell Lysis

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

PATHWAYS OF COMPLEMENT ACTIVATION



ARTICLE IN PRESS
KI REPORTS
KIReports.org
CLINICAL RESEARCH

Safety, Tolerability and Efficacy of Narsoplimab, a Novel MASP-2 Inhibitor for the Treatment of IgA Nephropathy

Richard A. Lafayette[1], Brad H. Rovin[2], Heather N. Reich[3], James A. Tumlin[4], Jürgen Floege[5] and Jonathan Barratt[6]

[1]Division of Nephrology, Department of Medicine, Stanford University, Stanford, California, USA; [2]Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [3]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [4]NephroNet Clinical Research Consortium, Atlanta, Georgia, USA; [5]Department of Nephrology and Clinical Immunology, RWTH Aachen University Hospital, Aachen, Germany; and [6]Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

Introduction: Narsoplimab is a human monoclonal antibody against mannan-associated lectin-binding serine protease-2 (MASP-2). Now in a phase 3 study, narsoplimab was evaluated in a staged phase 2 study assessing safety and effectiveness in high-risk patients with IgA nephropathy (IgAN).

Methods: Substudy 1 was a single-arm open-label study of 12 weekly infusions and tapered corticosteroids, with 6 weeks of follow-up. In substudy 2, patients were randomized 1:1 to receive a course of treatment consisting of once-weekly narsoplimab or vehicle infusions for 12 weeks. After 6 weeks of follow-up, both substudy 2 groups could continue in an open-label extension, receiving 1 or more narsoplimab courses at the investigator's discretion.

Results: The most commonly reported adverse events (AEs) included headache, upper respiratory infection, and fatigue. Most AEs were mild or moderate and transient. No treatment-related serious AEs were reported. All 4 patients who were enrolled in substudy 1 had reductions in 24-hour urine protein excretion (UPE) at week 18, ranging from 54% to 95% compared with baseline. In substudy 2, the vehicle and narsoplimab groups had similar proteinuria reductions at week 18. Eight patients (3 vehicle, 5 narsoplimab) continued in the dosing extension; all received narsoplimab. Median reduction in 24-hour UPE in these 8 patients was 61.4% at 31 to 54 weeks postbaseline. Estimated glomerular filtration rates (eGFR) remained stable in both substudies.

Conclusion: This interim analysis suggests that narsoplimab treatment is safe, is well tolerated, and may result in clinically meaningful reductions in proteinuria and stability of eGFR in high-risk patients with advanced IgAN.

Kidney Int Rep (2020) ■, ■–■; https://doi.org/10.1016/j.ekir.2020.08.003
KEYWORDS: complement system; IgA nephropathy; lectin pathway; mannan-associated lectin-binding serine protease-2; MASP-2; narsoplimab

IgA nephropathy (IgAN) is the most common primary glomerular disease, with a global incidence of at least 2.5 per 100,000 per year.[1] The clinical course of IgAN is heterogenous, but up to 40% of IgAN patients develop end-stage kidney disease (ESKD) within 20 years of diagnosis.[2] There are no therapies approved specifically for the treatment of IgAN. Given the conflicting results of many studies of this disease, treatment is customized to individual patients depending on clinical presentation. Currently, management of patients includes treatment with renin–angiotensin system blockade to lower blood pressure and to decrease proteinuria. Corticosteroids and other immunosuppressive agents are variably used when significant proteinuria persists despite renin–angiotensin system blockade, with inconsistent results and significant toxicity.

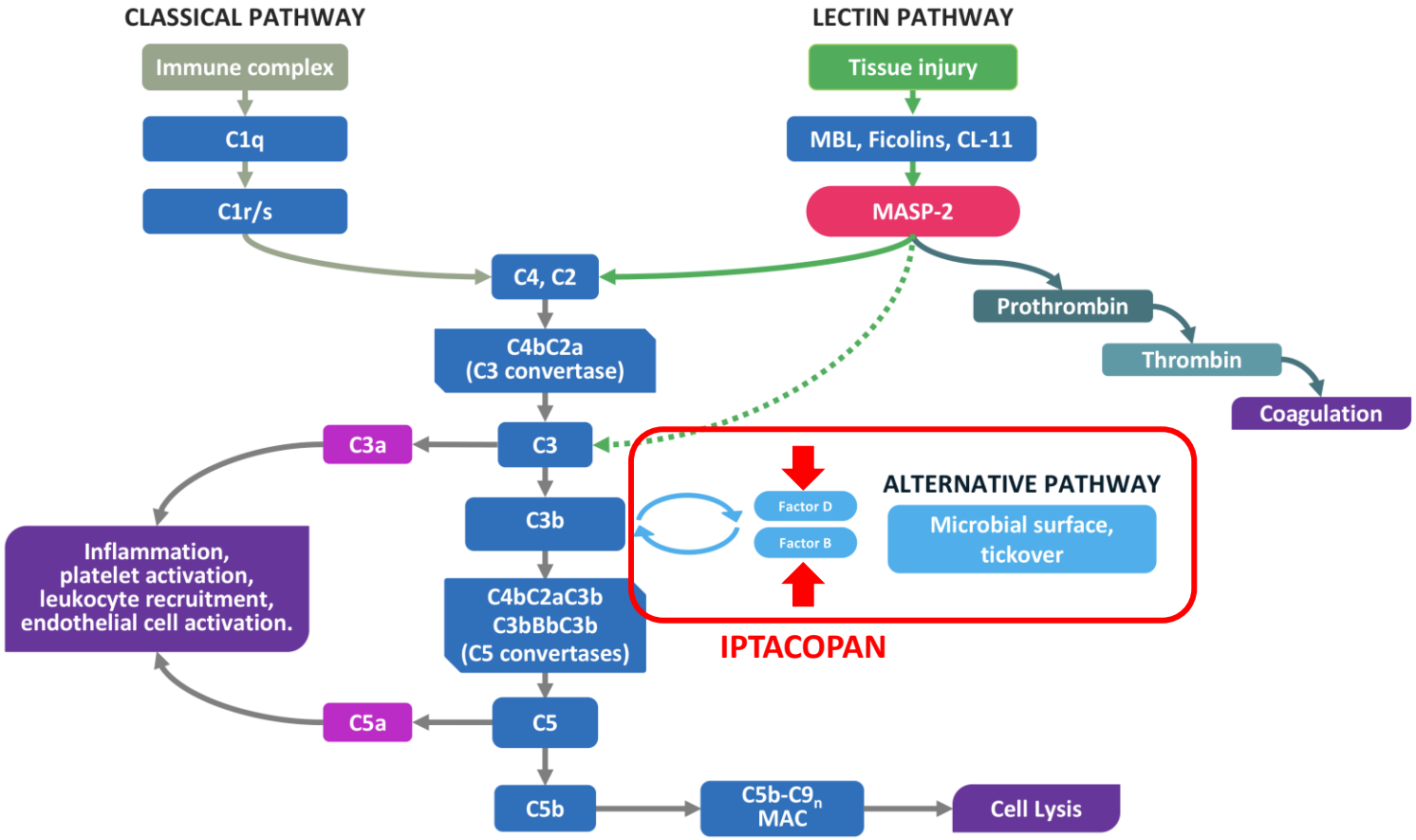
To improve IgAN outcomes, targeted interventions are necessary. Mounting pathologic, biochemical, experimental, and genetic findings support a pivotal role of complement activation in disease onset and progression of IgAN. Activation of the alternative and lectin pathways have been implicated in IgAN.[3] Immunohistochemical findings of C3, properdin, C4d, mannan-binding lectin (MBL), and C5b-9 deposits in

Correspondence: Richard A. Lafayette, Division of Nephrology, Department of Medicine, Stanford University, Stanford, California 94305, USA. E-mail: lazar@stanford.edu
Received 27 May 2020; revised 11 July 2020; accepted 4 August 2020; published online 13 August 2020

UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

PATHWAYS OF COMPLEMENT ACTIVATION



Final 12-week Endpoint Analyses of a Phase 2 Dose-Ranging Study to Investigate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy

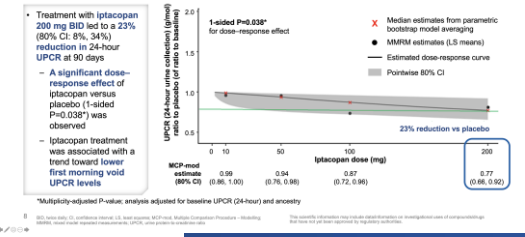
Professor Jonathan Barratt

on behalf of the Iptacopan IgAN Program Steering Committee

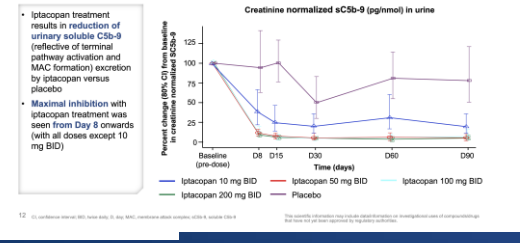
University of Leicester & John Walls Renal Unit, Leicester, UK

58th ERA-EDTA Congress, Berlin, June 5–8, 2021

Iptacopan showed dose-dependent reduction in proteinuria at Day 90 versus placebo

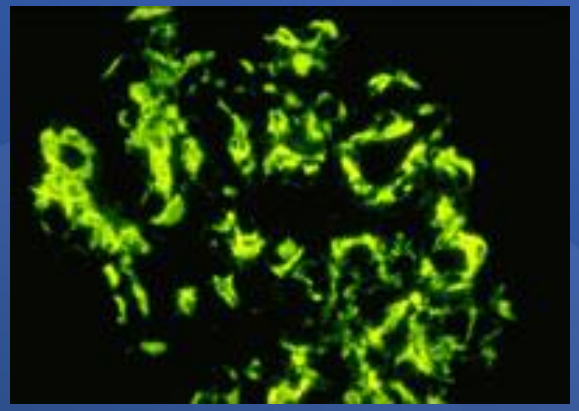


Iptacopan reduces levels of alternative pathway biomarkers in urine



UNIVERSITY OF LEICESTER

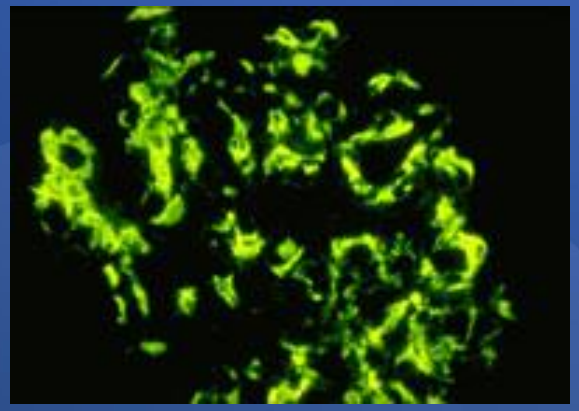
Leicester IgA Nephropathy Research Group



THE NEXT 10 YEARS

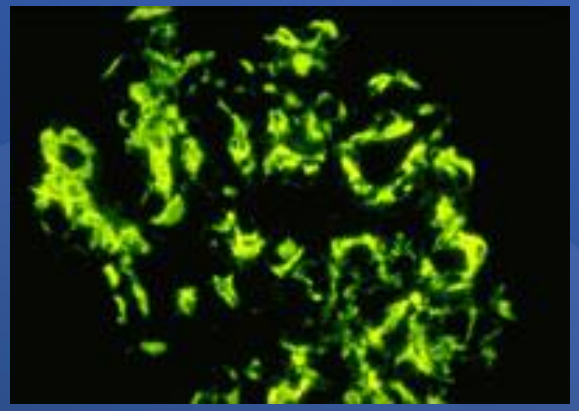
UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group



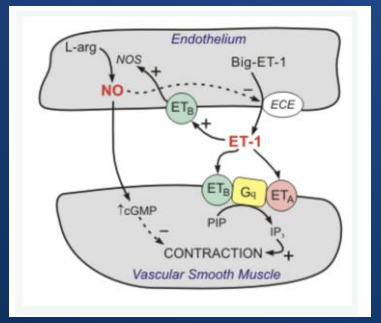
UNIVERSITY OF LEICESTER

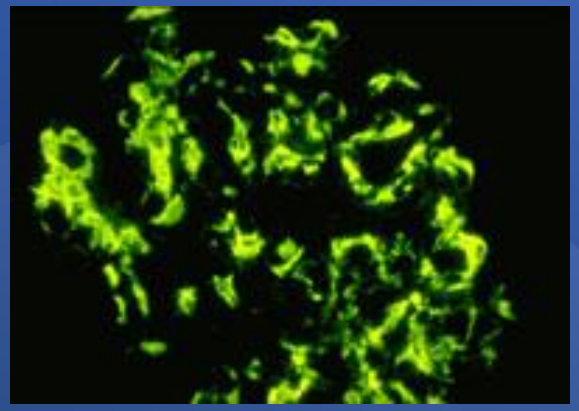
Leicester IgA Nephropathy Research Group

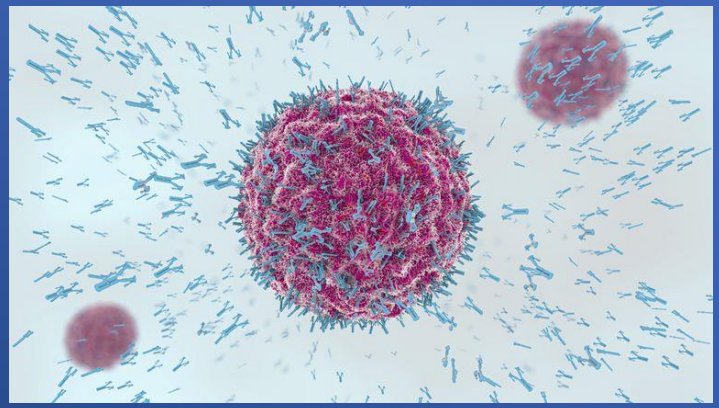


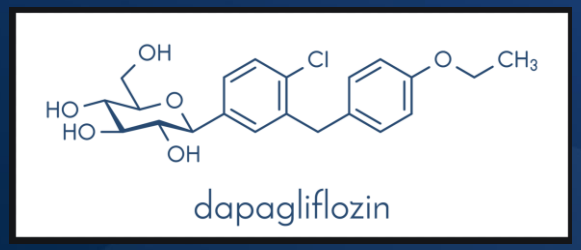
UNIVERSITY OF LEICESTER

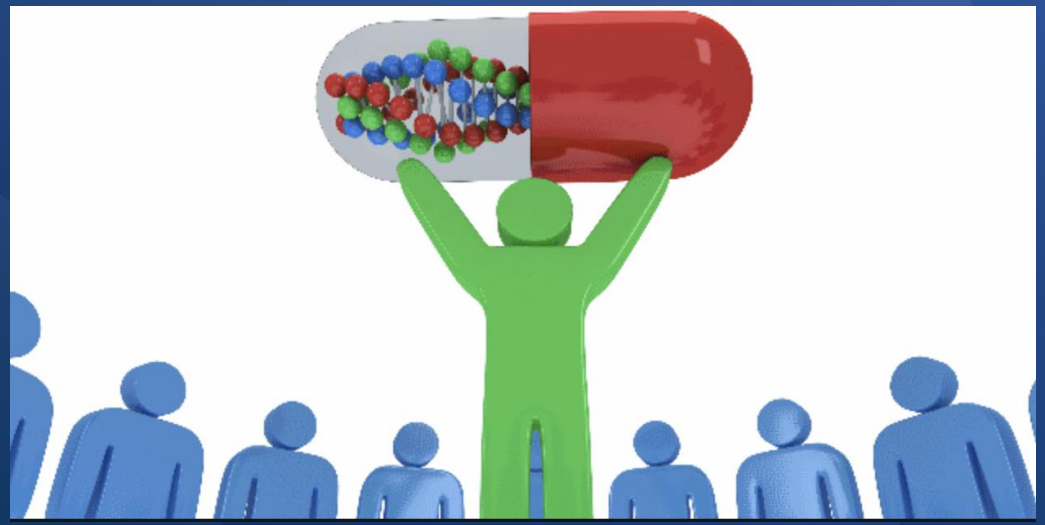
Leicester IgA Nephropathy Research Group



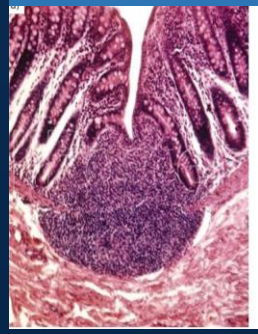


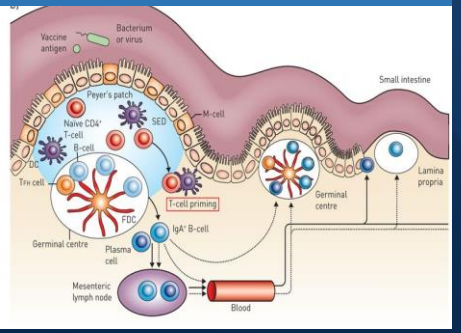


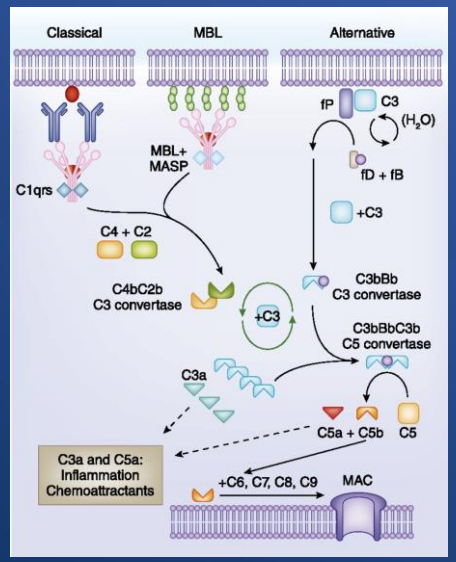




Mucosa Associated Lymphoid Tissue







Agenda

Welcome
- Chris Brickley – Associate Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

Overview of Cemdisiran Program
- Sonalee Agarwal, Ph.D. – Vice President and Program Leader, Cemdisiran

IgAN Disease Background, Treatment Landscape, and Unmet Need
- Jonathan Barratt, Ph.D., FRCP – The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences; Honorary Consultant Nephrologist, The John Walls Renal Unit, Leicester General Hospital

Cemdisiran Phase 2 Data
- Ishir Bhan, M.D., MPH – Senior Director, Clinical Research

Q&A Session

Cemdisiran Phase 2 Study Design

Randomized, Double-Blind Study in Patients with IgA Nephropathy

Patient Population
N=31

- Primary IgAN with hematuria (biopsy-proven)
- Persistent proteinuria (≥1 g / 24 h)
- eGFR ≥30 mL/min/1.73 m^2
- Stable optimal treatment (ACEi or ARBs) for at least 3 months
- No recent steroid or other immunosuppressive treatment (past 6 months)

Run-in Period (SOC for 14 weeks)[a]

2:1 RANDOMIZATION[b]

0 — 32 — 36
Treatment Period (wks)

Cemdisiran
600 mg SQ q4w
+ SOC

or

Placebo
SQ q4w
+ SOC

Week 32 Assessment

Primary Endpoint:
- % change from baseline in 24h UPCR

Select Secondary Endpoints:
- % change from baseline in 24-h UP
- Change from baseline in UPCR as measured by spot urine
- Incidence of AEs[c]

Select Exploratory Endpoints:
- Change from baseline in eGFR
- Change from baseline in renal damage and inflammation markers[c]
- Change from baseline in complement activity[c]

Open Label Extension Period (156 weeks)

[a]During the run-in period, patients' blood pressure, kidney function, hematuria, proteinuria, and treatment with SOC will be documented by the Investigator. SOC was considered to be ACEi or ARB. Patients with proteinuria ≥1 g/24 h within 2 weeks of the end of the run-in period, and who meet blood pressure and eGFR criteria, will be eligible to roll into the treatment period. [b]Stratified by baseline urine proteinuria levels (≥1 g/24 h and <2 g/24 h versus ≥2 g/24 h). [c]Monitored during the course of the study.

Immunization for encapsulated organisms are provided prior to treatment initiation to reduce the risk of infection associated with C5 inhibition.

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; q4w, every 4 weeks; SOC, standard of care; SQ, subcutaneously; UP, urine protein; UPCR, urine protein to creatinine ratio

Demographic and Baseline Disease Characteristics

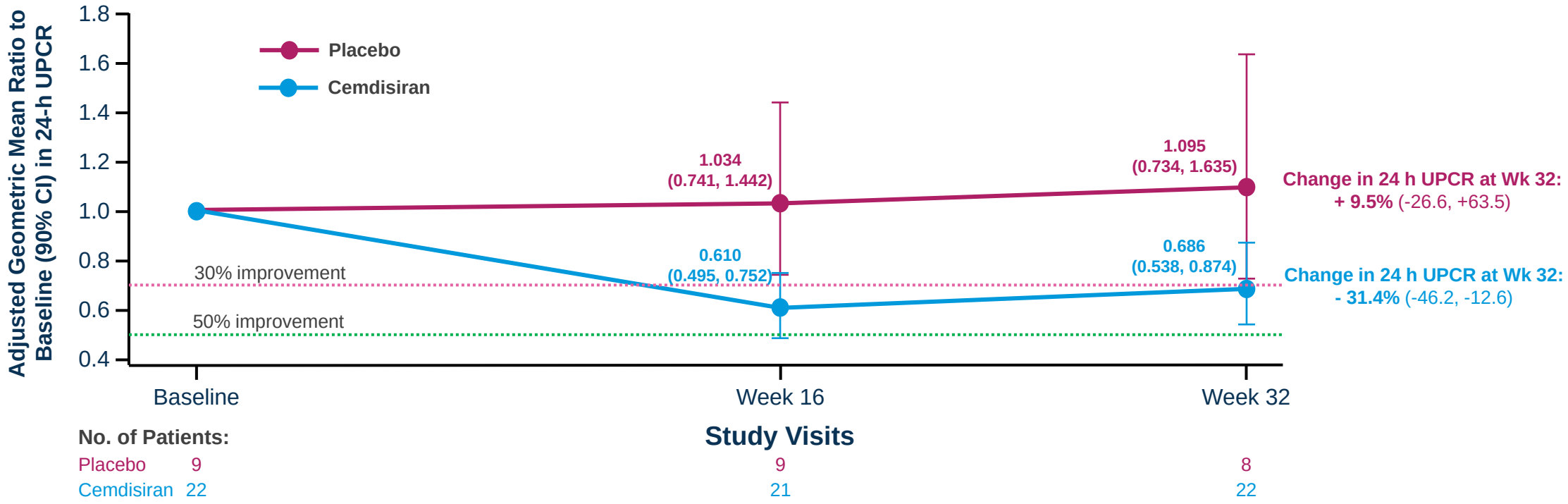
Baseline Demographic and Disease Characteristics Largely Similar Between Treatment Groups

	Placebo (N=9)	Cemdisiran (N=22)
Age, mean (SD) (years)	37.6 (10.4)	40.5 (10.1)
Male, n (%)	3 (33.3)	13 (59.1)
Race, n (%) Asian White Other/Missing	 4 (44.4) 4 (44.4) 1 (11.1)	 12 (54.5) 8 (36.4) 2 (9.1)
BMI, mean (SD) (kg/m^2)	26.8 (4.9)	30.4 (5.3)
Time since diagnosis, median (IQR) (years)	2.5 (4.6)	1.8 (1.9)
Systolic blood pressure, mean (SD) (mmHg)	116.1 (7.2)	125.0 (11.7)
Diastolic blood pressure, mean (SD) (mmHg)	68.0 (12.9)	79.8 (7.9)
24-hour UP, mean (SD) (g/24 hr)	2.9 (1.3)	2.5 (1.5)
24-hour UPCR, mean (SD) (g/g)	2.0 (0.8)	1.6 (1.0)
eGFR, mean (SD) ($mL/min/1.73\ m^2$)	61 (33)	72 (27)
Number of patients on background ACEi or ARB	8 (88.9)	21 (95.5)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; UP, urine protein; UPCR, urine protein to creatinine ratio.

Cemdisiran Treatment Led to Clinically Meaningful Proteinuria Reduction Compared with Placebo at Week 32

- Primary endpoint of change from baseline in 24-hour UPCR compared with placebo at Week 32 was **-37.4%** (90% CI: -61.0, 0.5)[a]
- Secondary endpoint of change from baseline in 24-hour urine total protein compared with placebo at Week 32 was **-36.2%** (90% CI: -61.6, 6.0)[a] (data not shown)



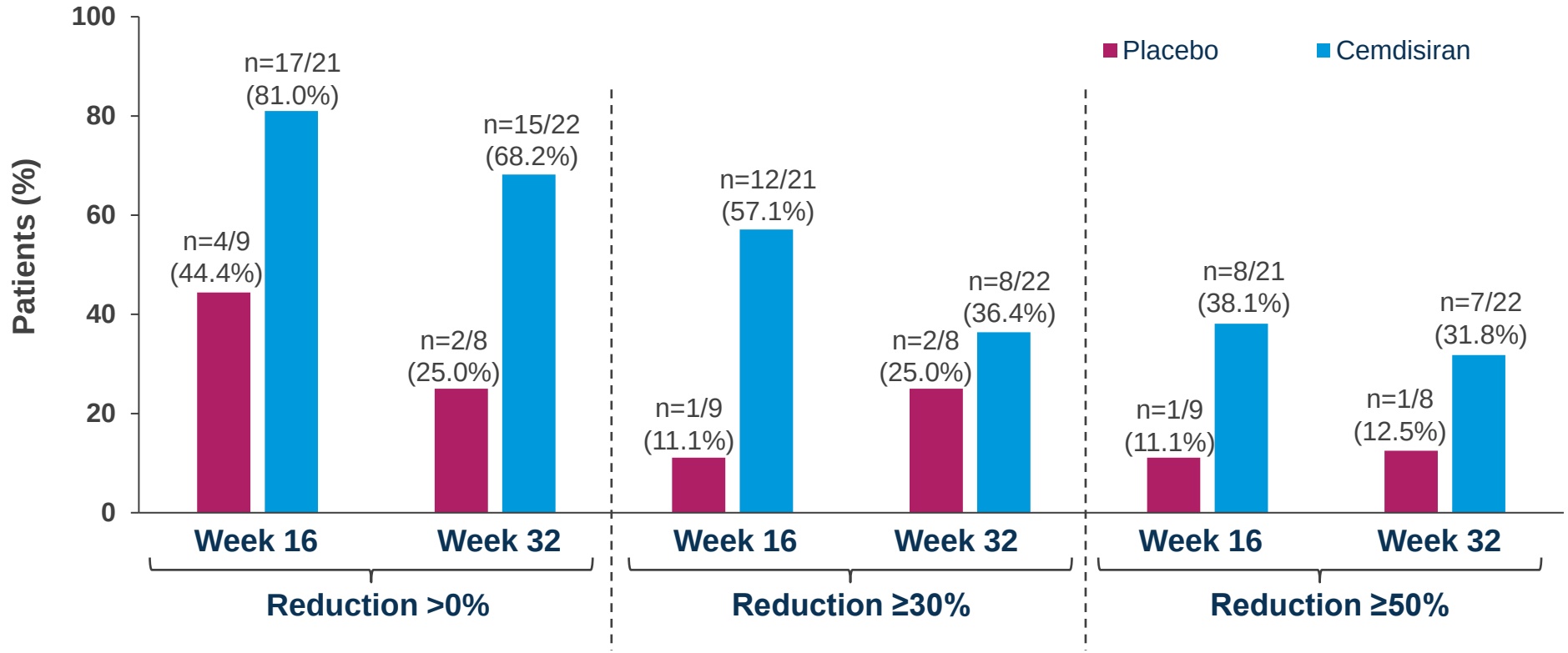
[a]Placebo-adjusted geometric mean percent change and 90% CI. A mixed-effect model repeated-measures approach was adopted, where the outcome variable was analyzed in log-scale and the model included fixed effects of treatment, scheduled visits, interaction term of treatment and scheduled visits, baseline 24-hour UPCR in log-scale, and patient as a random effect; the model-based least squares mean difference was then transformed back to the original UPCR scale. UPCR by spot urine at Week 32 was analyzed in a similar manner as appropriate. Negative numbers reflect a decrease in proteinuria. This Phase 2 study was descriptive only and did not include statistical hypothesis testing. At baseline, the mean (SD) 24-hour UPCR (g/g) values were 1.8 (1.2) in the cemdisiran group and 2.0 (0.8) in the placebo group.

CI, confidence interval; UPCR, urine protein to creatinine ratio

Higher Proportion of Patients Demonstrated Reductions in 24-hour UPCR with Cemdisiran at Clinically Relevant Thresholds Compared with Placebo at Week 32

- **31.8%** of patients treated with cemdisiran achieved ≥50% reduction in 24-hour UPCR at Week 32, compared with 12.5% of placebo-treated patients[a]

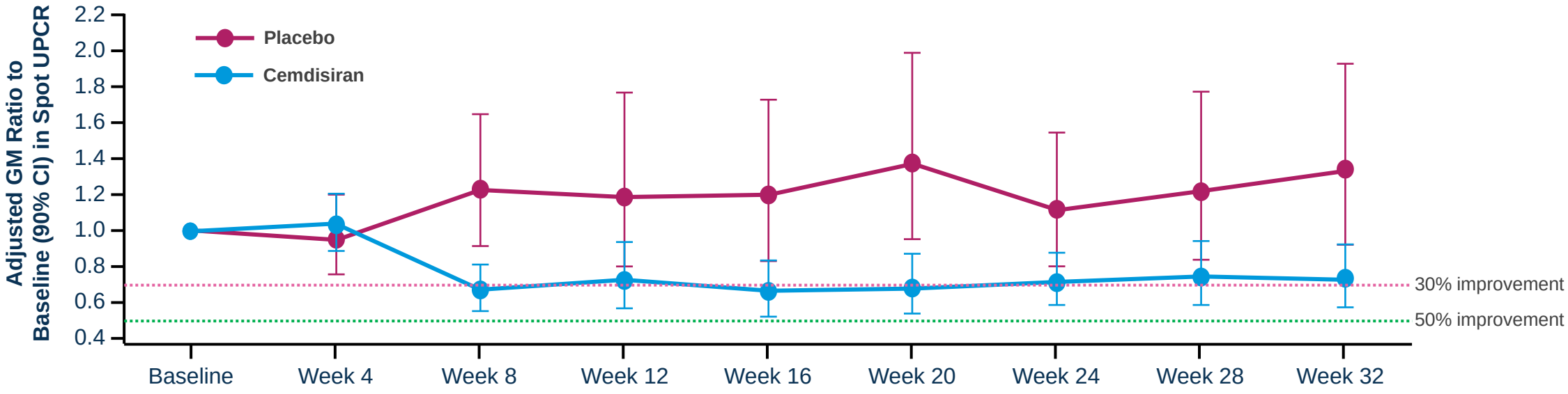
Proportion of Patients Achieving 24-hour UPCR Thresholds



[a]This Phase 2 study was descriptive only and did not include statistical hypothesis testing.
UPCR, urine protein to creatinine ratio.

Cemdisiran Treatment Led to Clinically Meaningful Reduction in Spot UPCR Compared with Placebo at Week 32

- Secondary endpoint of change from baseline in spot UPCR compared with placebo at Week 32 was **-45.8%** (90% CI: -60.1, -26.3)[a]
- Monthly spot UPCR assessment of proteinuria shows similar evidence of efficacy to 24-hour UPCR, with onset of effect by Week 8 that remained stable over time



No. of Patients:

Placebo	9	9	9	8	9	9	8	7	8
Cemdisiran	22	21	20	20	21	22	20	19	20

[a]Adjusted geometric mean percent change and 90% CI. Negative numbers reflect a decrease in proteinuria. This Phase 2 study was descriptive only and did not include statistical hypothesis testing.
At baseline, the mean (SD) baseline spot UPCR (g/g) values were 1.8 (2.1) in the cemdisiran group and 1.9 (1.2) in the placebo group.
CI, confidence interval; UPCR, urine protein to creatinine ratio.

Cemdisiran Phase 2 IgAN Safety Summary

Double-Blind Period

- No AEs led to treatment or study discontinuation
- One death occurred in cemdisiran treatment arm due to cardiorespiratory collapse and was not considered related to study drug
  - Considered both a serious and a severe AE (see table), which occurred due to post-operative complications following bypass surgery
- Two treatment interruptions occurred in cemdisiran arm (9.1%); both were considered related to study drug
  - One patient (4.5%) had urticaria and one patient (4.5%) had an atopic dermatitis flare-up
- AEs ≥10% in cemdisiran arm included injection-site reactions (ISRs, 40.9%) and peripheral edema (13.6%)
  - Majority of ISRs were mild and transient; peripheral edema was reported as mild and not related to cemdisiran
- No safety signals regarding liver function tests[d], hematology, or renal function related to cemdisiran

Cemdisrian Phase 2 IgAN Safety Summary[a]

At least one treatment emergent adverse event, n (%)	Placebo (N=9)	Cemdisiran (N=22)
AEs	8 (88.9)	19 (86.4)
Serious AEs	0	1 (4.5)
Severe AEs	0	1 (4.5)
AEs leading to treatment interruption	1 (11.1)	2 (9.1)[b]
AEs leading to treatment discontinuation	0	0
Death[c]	0	1 (4.5)

[a]Treatment-emergent AEs includes events occurring or worsening on or after the first dose of study drug and through 28 days after the last dose or any study drug related AEs. AEs with missing causality are considered related. AEs with missing severity are considered severe. [b]Both treatment interruptions in the cemdisiran arm were transient. [c]All fatal AEs are summarized regardless of treatment-emergent classification. dTransient elevations in ALT and AST were observed with cemdisiran treatment, however, there were no safety concerns.

AE, adverse event; ISR, injection-site reaction.

Summary of Phase 2 Study Results

- Monthly subcutaneous doses of cemdisiran led to clinically meaningful reduction in 24-hour UPCR observed at Week 32 relative to placebo
  - 37.4% reduction in 24-hour UPCR observed at Week 32 relative to placebo
  - 31.8% of patients treated with cemdisiran (vs 12.5% of placebo-treated patients) achieved ≥50% reduction in 24-hour UPCR at Week 32
- Spot urine data are consistent with 24-hour urine data and remain stable over time, with initial treatment effect emerging at Week 8
- Cemdisiran was generally well tolerated in patients with IgAN
  - The most frequent adverse events were injection site reactions and peripheral edema
  - No AEs led to treatment or study discontinuation
- These data support further evaluation of cemdisiran as potential therapy in IgAN

Thank you to the patients, their families, investigators, study staff, and collaborators for their continued participation in the cemdisiran Phase 2 IgAN study

IgAN, immunoglobulin A nephropathy; UPCR, urine protein to creatinine ratio

Developing Cemdisiran in Complement-Mediated Diseases

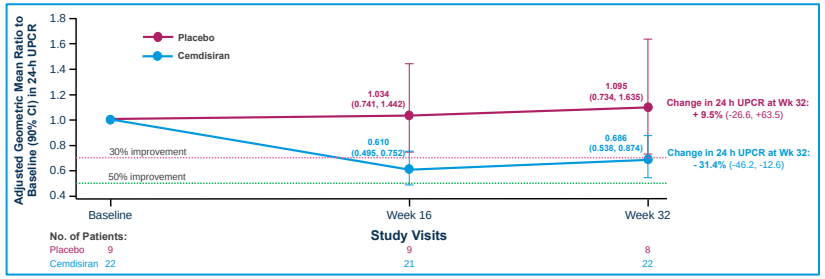
Potentially Meaningful Opportunity for RNAi Therapeutic Delivering Sustained C5 Suppression Alone or in Combination

IgAN

- Most common primary chronic glomerular disease, affecting ~350,000 – 450,000 in US, EU, & Japan*[1-5]
- Limited treatment options
- Known complement involvement in disease pathology

Phase 2 IgAN Results

- Clinically meaningful results across multiple endpoints



- Cemdisiran was generally well tolerated in patients with IgAN

Next Steps

- Additional Phase 2 analyses to be presented at future conference
- Phase 3 study preparations in progress
- Ongoing development by partner, Regeneron, in PNH and MG

*Based on Alnylam internal calculations

1. Kwon CS, et al. J Health Econ Outcomes Res. 8(2):36-45.; 2. Schena FP, et al. Semin Nephrol. 2018;38(5):435-442.; 3. Census Population Clock. Census.gov. September 14, 2022.; 4. Moriyama T, et al. PLoS ONE. 2014;9(3):e91756.; 5. Alnylam Pharmaceuticals, Data on File.

Agenda

Welcome
- Chris Brickley – Associate Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

Overview of Cemdisiran Program
- Sonalee Agarwal, Ph.D. – Vice President and Program Leader, Cemdisiran

IgAN Disease Background, Treatment Landscape, and Unmet Need
- Jonathan Barratt, Ph.D., FRCP – The Mayer Professor of Renal Medicine Department of Cardiovascular Sciences; Honorary Consultant Nephrologist, The John Walls Renal Unit, Leicester General Hospital

Cemdisiran Phase 2 Data
- Ishir Bhan, M.D., MPH – Senior Director, Clinical Research

Q&A Session

Upcoming RNAi Roundtables

Alnylam Engine for Sustainable Innovation: Leadership in RNAi Platform and Human Genetics

Friday, October 21, 10:00 am ET

CNS Delivery and ALN-APP, in Development for the Treatment of Alzheimer's Disease and Cerebral Amyloid Angiopathy

Tuesday, November 1, 11:00 am ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, https://capella.alnylam.com

Save the date!

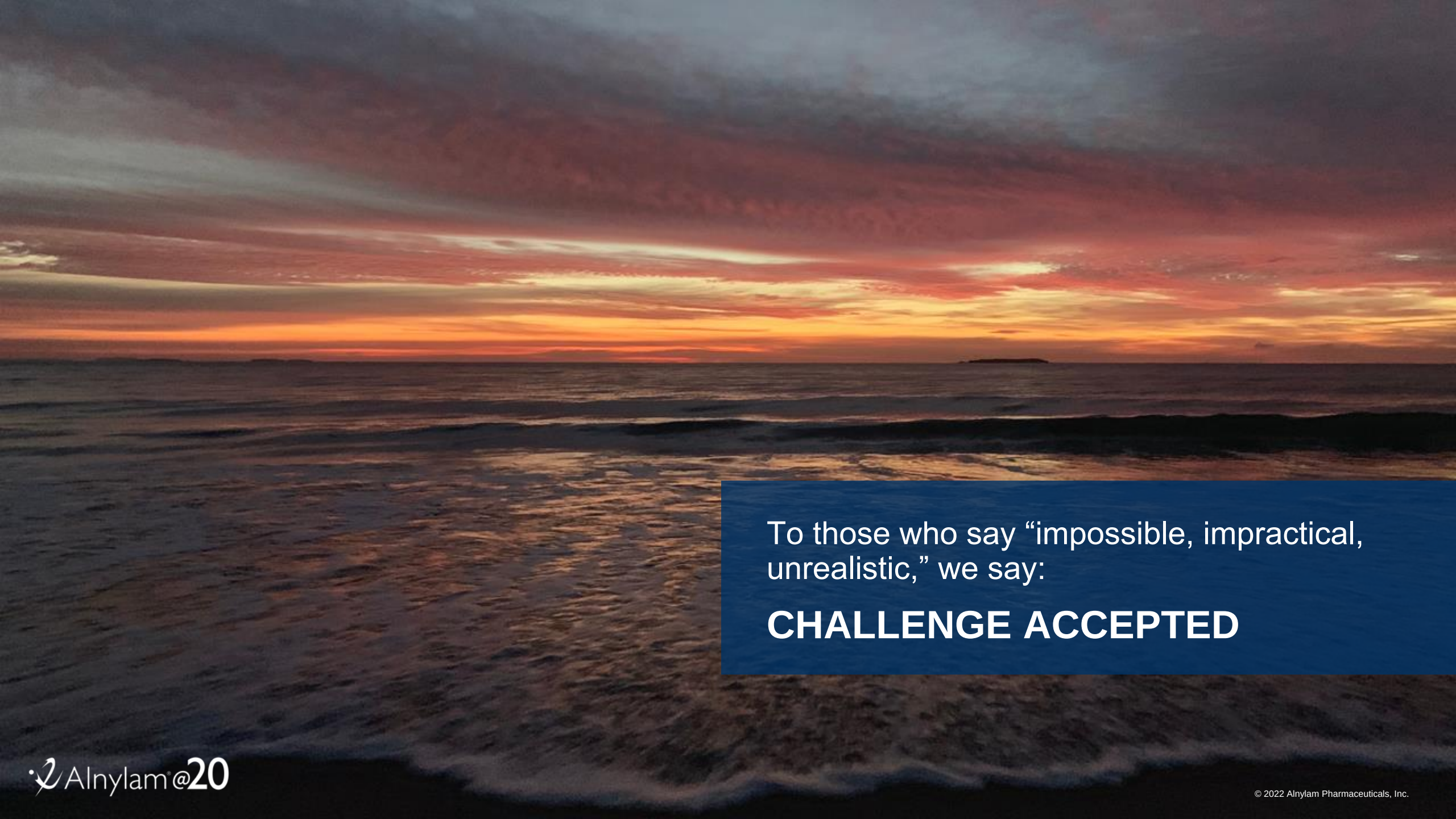
Alnylam®

R&D Day

December 15, 2022

A VIRTUAL EVENT

Registration information
coming soon.



Alnylam@20